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(54) Title: PIPERAZINE, [1,4]DIAZEPANE, [1,4]DIAZOCANE, AND [1,5]DIAZOCANE FUSED IMIDAZO RING COMPOUNDS

(57) Abstract: Piperazine, [1,4]diazepane, [1,4]diazocane, and [1,5]diazocane fused imidazo ring compounds (i.e., imidazoquinolines, tetrahydroimidazoquinolines, imidazonaphthyridines, tetrahydroimidazonaphthyridines, and imidazopyridines), pharmaceutical compositions containing the compounds, intermediates, methods of making, and methods of use of these compounds as immunomodulators, for inducing or inhibiting cytokine biosynthesis in animals and in the treatment of diseases including viral and neoplastic diseases are disclosed.

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PIPERAZINE, [1,4]DIAZEPANE, [1,4]DIAZOCANE, AND [1,5]DIAZOCANE FUSED IMIDAZO RING COMPOUNDS

RELATED APPLICATIONS

The present invention claims priority to U.S. Provisional Application Serial No. 60/533,024, filed 12/29/2003, which is incorporated herein by reference.

BACKGROUND

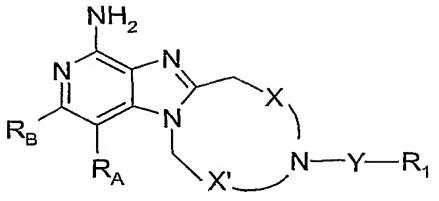
In the 1950's the 1*H*-imidazo[4,5-*c*]quinoline ring system was developed, and 1-(6-methoxy-8-quinolinyl)-2-methyl-1*H*-imidazo[4,5-*c*]quinoline was synthesized for possible use as an antimalarial agent. Subsequently, syntheses of various substituted 1*H*-imidazo[4,5-*c*]quinolines were reported. For example, 1-[2-(4-piperidyl)ethyl]-1*H*-imidazo[4,5-*c*]quinoline was synthesized as a possible anticonvulsant and cardiovascular agent. Also, several 2-oxoimidazo[4,5-*c*]quinolines have been reported.

Certain 1*H*-imidazo[4,5-*c*]quinolin-4-amines and 1- and 2-substituted derivatives thereof were later found to be useful as antiviral agents, bronchodilators and immunomodulators. Subsequently, certain substituted 1*H*-imidazo[4,5-*c*]pyridin-4-amine, quinolin-4-amine, tetrahydroquinolin-4-amine, naphthyridin-4-amine, and tetrahydronaphthyridin-4-amine compounds as well as certain analogous thiazolo and oxazolo compounds were synthesized and found to be useful as immune response modifiers, rendering them useful in the treatment of a variety of disorders.

There continues to be interest in and a need for compounds that have the ability to modulate the immune response, by induction and/or inhibition of cytokine biosynthesis or other mechanisms.

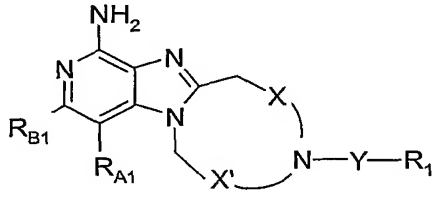
SUMMARY

The present invention provides a new class of compounds that are useful in inducing cytokine biosynthesis in animals. Such compounds are of the following Formula I:



I

and, more particularly, compounds are of the following Formula II:



II

wherein R_1, R_A, R_B, R_{A1}, R_{B1}, X, X', and Y are as defined below.

The compounds of Formula I and more particularly Formula II are useful as immune response modifiers (IRMs) due to their ability to induce and/or inhibit cytokine biosynthesis (e.g., induce and/or inhibit the biosynthesis or production of one or more cytokines) and otherwise modulate the immune response when administered to animals. Compounds can be tested per the test procedures described in the Examples Section. Compounds can be tested for induction of cytokine biosynthesis by incubating human peripheral blood mononuclear cells (PBMC) in a culture with the compound(s) at a concentration range of 30 to 0.014 μM and analyzing for interferon (α) or tumor necrosis factor (α) in the culture supernatant. Compounds can be tested for inhibition of cytokine biosynthesis by incubating mouse macrophage cell line Raw 264.7 in a culture with the compound(s) at a single concentration of, for example, 5 μM and analyzing for tumor necrosis factor (α) in the culture supernatant. The ability to modulate cytokine biosynthesis, for example, induce the biosynthesis of one or more cytokines, makes the compounds useful in the treatment of a variety of conditions such as viral diseases and neoplastic diseases, that are responsive to such changes in the immune response.

The invention further provides pharmaceutical compositions containing an effective amount of a compound of Formula I and methods of inducing cytokine biosynthesis in an animal, treating a viral infection and/or treating a neoplastic disease in an animal by administering an effective amount of a compound of Formula I to the animal.

In addition, methods of synthesizing compounds of Formula I and Formula II and intermediates useful in the synthesis of these compounds are provided.

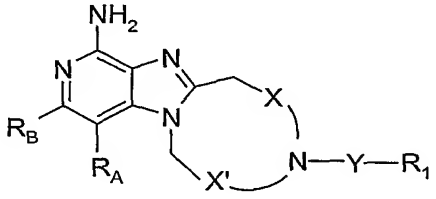
As used herein, "a," "an," "the," "at least one," and "one or more" are used interchangeably.

The terms "comprises" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. In several places throughout the description, guidance is provided through lists of examples, which examples can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

The present invention provides compounds of the following Formulas I through VII:



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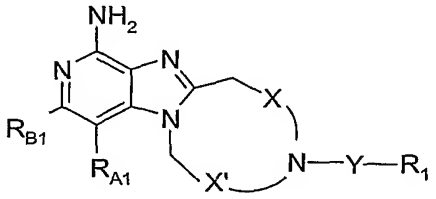
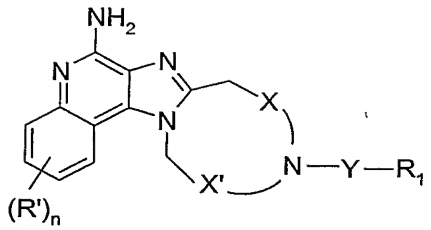
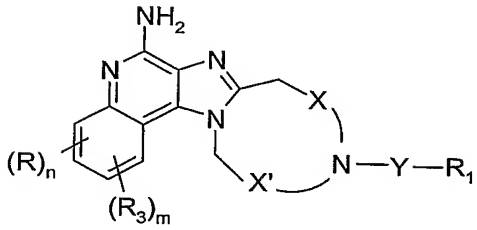


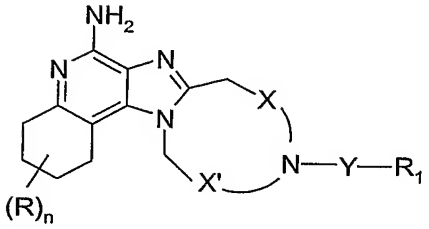
II



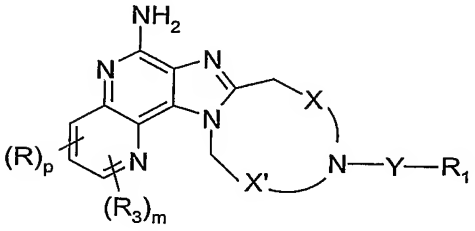
III



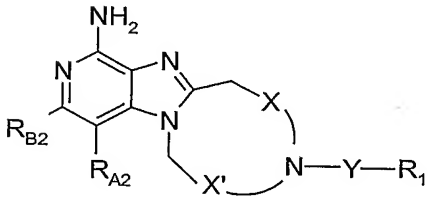
IV



V



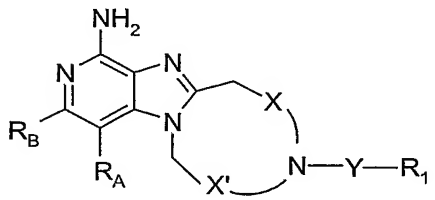
VI



VII

wherein R_1, R_3, R, R', R_A, R_B, R_{A1}, R_{B1}, R_{A2}, R_{B2}, X, X', Y, m, n, and p are as defined below.

In one embodiment, the present invention provides a compound of Formula I:



I

wherein:

R_A and R_B are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

or when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R' groups;

or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

X is a bond or a straight or branched chain C_{1-2} alkylene;

X' is a straight or branched chain C_{1-8} alkylene optionally substituted with hydroxy, $-O-R_{11}$, or one or more halogen atoms wherein the hydroxy, $-O-R_{11}$, or one or more halogen atoms are bonded to a carbon atom other than a carbon atom adjacent to a nitrogen atom;

X and X' are further characterized in that the total number of ring carbon atoms contributed by X and X' is 1 to 3;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-C(R_6)-N(R_8)-$,

$-C(R_6)-N(R_8)-C(R_6)-$, and

$-C(R_6)-N(R_8)-S(O)_2-$;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_1 is selected from the group consisting of: hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, alkanoyl, alkanoyloxy, alkoxycarbonyl, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylthio, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, and in the case of aryl, methylenedioxy; further with the proviso that when R_A and R_B together form a fused benzene ring that is unsubstituted or substituted by C_{1-4} alkyl, C_{1-4} alkoxy, or halogen, and Y is a bond, R_1 is not hydrogen or C_{1-4} alkyl;

R_6 is selected from the group consisting of =O and =S;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

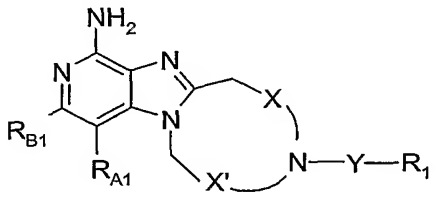
R_9 is selected from the group consisting of hydrogen and alkyl;

R_{11} is selected from the group consisting of C_{1-6} alkyl and $-Si(C_{1-6}$ alkyl$)_3$; and

R' is a non-interfering substituent;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a compound of Formula II:



II

wherein:

R_{A1} and R_{B1} are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

or when taken together, R_{A1} and R_{B1} form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group;

or when taken together, R_{A1} and R_{B1} form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

X is a bond or a straight or branched chain C_{1-2} alkylene;

X' is a straight or branched chain C_{1-8} alkylene optionally substituted with hydroxy, $-O-R_{11}$, or one or more halogen atoms wherein the hydroxy, $-O-R_{11}$, or one or more

halogen atoms are bonded to a carbon atom other than a carbon atom adjacent to a nitrogen atom;

X and X' are further characterized in that the total number of ring carbon atoms contributed by X and X' is 1 to 3;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-C(R_6)-N(R_8)-$,

$-C(R_6)-N(R_8)-C(R_6)-$, and

$-C(R_6)-N(R_8)-S(O)_2-$;

R_1 is selected from the group consisting of: hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, alkanoyl, alkanoyloxy, alkoxycarbonyl, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylthio, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, and in the case of aryl, methylenedioxy; further with the proviso that when R_{A1} and R_{B1} together form a fused benzene ring that is unsubstituted or substituted by C_{1-4} alkyl, C_{1-4} alkoxy, or halogen, and Y is a bond, R_1 is not hydrogen or C_{1-4} alkyl;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_3 is selected from the group consisting of:

$-Z-R_4$,

$-Z-X''-R_4$,

$-Z-X''-Y'-R_4$,

$-Z-X''-Y'-X''-Y'-R_4$, and

$-Z-X''-R_5$;

X'' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y' is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

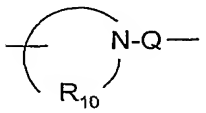
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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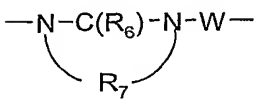

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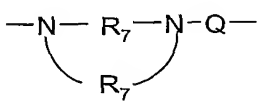

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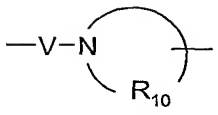
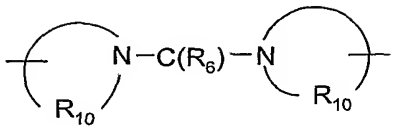


, and

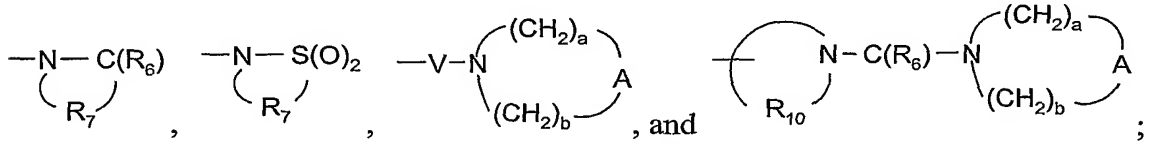


;

Z is a bond or -O-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

R_{11} is selected from the group consisting of C_{1-6} alkyl and $-Si(C_{1-6}\ alkyl)_3$;

A is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(R_6)-O-, and -C(R_6)-N(OR_9);

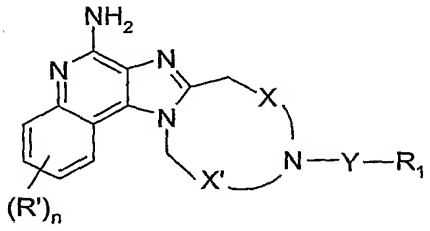
V is selected from the group consisting of -C(R_6)-, -O-C(R_6)-, -N(R_8)-C(R_6)-, and -S(O)$_2$-;

W is selected from the group consisting of a bond, -C(O)-, and –S(O)$_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a compound of Formula III:



III

wherein:

X is a bond or a straight or branched chain C_{1-2} alkylene;

X' is a straight or branched chain C_{1-8} alkylene optionally substituted with hydroxy wherein the hydroxy is bonded to a carbon atom other than a carbon atom adjacent a nitrogen atom;

X and X' are further characterized in that the total number of ring carbon atoms contributed by X and X' is 1 to 3;

Y is selected from the group consisting of:

a bond,

-S(O)$_2$-,

-S(O)$_2$-N(R_8)-,

-C(R_6)-,

-C(R_6)-N(R_8)-,

-C(R_6)-N(R_8)-C(R_6)-, and

-C(R_6)-N(R_8)-S(O)$_2$-;

R_1 is selected from the group consisting of: hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, alkanoyl, alkanoyloxy, alkoxycarbonyl, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylthio, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, and in the case of aryl, methylenedioxy; further with the proviso that when Y is a bond, R_1 is not hydrogen or C_{1-4} alkyl;

R_6 is selected from the group consisting of =O and =S;

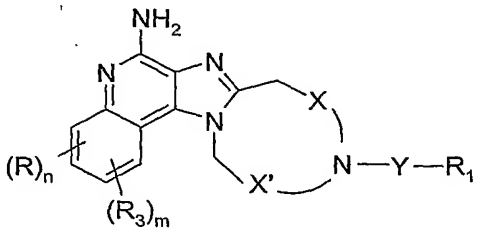
R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R' is a non-interfering substituent; and

n is an integer from 0 to 4;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a compound of Formula IV:



IV

wherein:

X is a bond or a straight or branched chain C_{1-2} alkylene;

X' is a straight or branched chain C_{1-8} alkylene optionally substituted with hydroxy, -O-R_{11}, or one or more halogen atoms wherein the hydroxy, -O-R_{11}, or one or more

halogen atoms are bonded to a carbon atom other than a carbon atom adjacent to a nitrogen atom;

X and X' are further characterized in that the total number of ring carbon atoms contributed by X and X' is 1 to 3;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-C(R_6)-N(R_8)-$,

$-C(R_6)-N(R_8)-C(R_6)-$, and

$-C(R_6)-N(R_8)-S(O)_2-$;

R_1 is selected from the group consisting of: hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, alkanoyl, alkanoyloxy, alkoxycarbonyl, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylthio, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, and in the case of aryl, methylenedioxy;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_3 is selected from the group consisting of:

$-Z-R_4$,

$-Z-X''-R_4$,

$-Z-X''-Y'-R_4$,

$-Z-X''-Y'-X''-Y'-R_4$, and

$-Z-X''-R_5$;

m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1;

n is an integer from 0 to 4;

X" is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y' is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

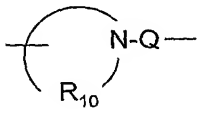
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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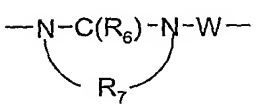

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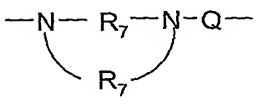

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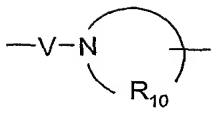
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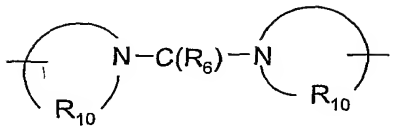
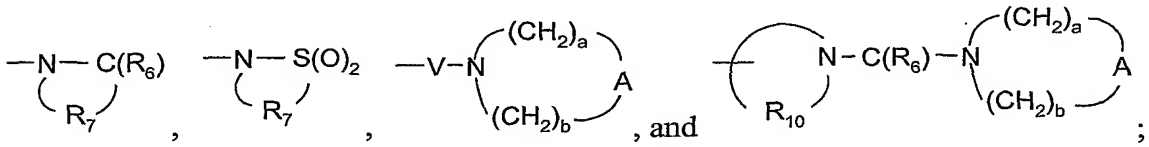

,

Z is a bond or -O-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of


;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

R_{11} is selected from the group consisting of C_{1-6} alkyl and $-Si(C_{1-6}$ alkyl$)_3$;

A is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(R_6)-O-, and -C(R_6)-N(OR_9);

V is selected from the group consisting of -C(R_6)-, -O-C(R_6)-, -N(R_8)-C(R_6)-, and -S(O)$_2$-;

W is selected from the group consisting of a bond, -C(O)-, and –S(O)$_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

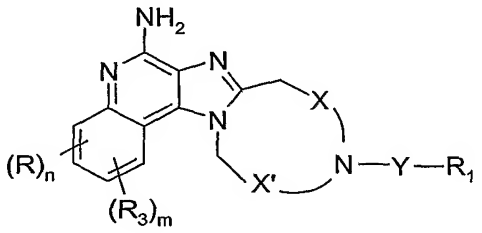
with the proviso that R_1 is not hydrogen or C_{1-4} alkyl when Y is a bond, and:

n and m are both 0, or

m is 0, n is 1, and R is selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, and halogen;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a compound of Formula IV:



IV

wherein:

X is a bond or a straight or branched chain C_{1-2} alkylene;

X' is a straight or branched chain C_{1-8} alkylene optionally substituted with hydroxy wherein the hydroxy is bonded to a carbon atom other than a carbon atom adjacent a nitrogen atom;

X and X' are further characterized in that the total number of ring carbon atoms contributed by X and X' is 1 to 3;

Y is selected from the group consisting of:

a bond,

-S(O)$_2$-,

-S(O)$_2$-N(R_8)-,

-C(R_6)-,

$-C(R_6)-N(R_8)-$,

$-C(R_6)-N(R_8)-C(R_6)-$, and

$-C(R_6)-N(R_8)-S(O)_2-$;

R_1 is selected from the group consisting of: hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, alkanoyl, alkanoyloxy, alkoxycarbonyl, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylthio, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, and in the case of aryl, methylenedioxy; further with the proviso that when Y is a bond, R_1 is not hydrogen or C_{1-4} alkyl;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_3 is selected from the group consisting of:

$-Z-R_4$,

$-Z-X''-R_4$,

$-Z-X''-Y'-R_4$,

$-Z-X''-Y'-X''-Y'-R_4$, and

$-Z-X''-R_5$;

m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1;

n is an integer from 0 to 4;

X" is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y' is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

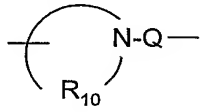
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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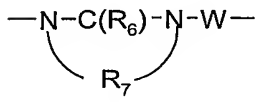

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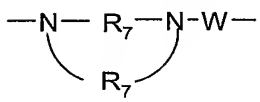

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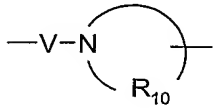
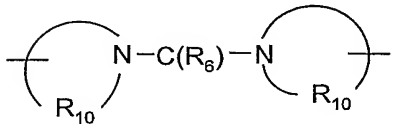


, and



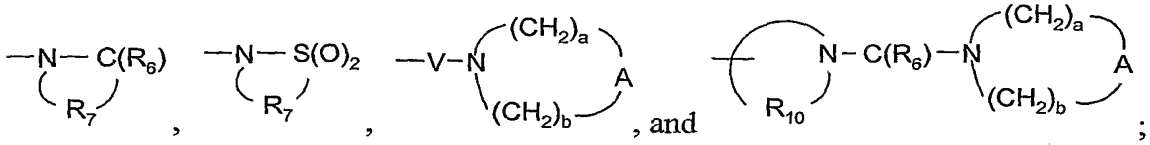
;

Z is a bond or -O-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl,

heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)$;

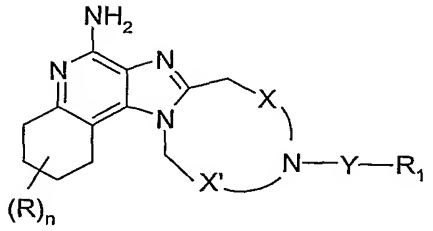
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a compound of Formula V:



V

wherein:

X is a bond or a straight or branched chain C_{1-2} alkylene;

X' is a straight or branched chain C_{1-8} alkylene optionally substituted with hydroxy, -O-R_{11}, or one or more halogen atoms wherein the hydroxy, -O-R_{11}, or one or more halogen atoms are bonded to a carbon atom other than a carbon atom adjacent to a nitrogen atom;

X and X' are further characterized in that the total number of ring carbon atoms contributed by X and X' is 1 to 3;

Y is selected from the group consisting of:

a bond,

-$S(O)_2$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-$C(R_6)$-$N(R_8)$-,

-$C(R_6)$-$N(R_8)$-$C(R_6)$-, and

-$C(R_6)$-$N(R_8)$-$S(O)_2$-;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

-$N(R_9)_2$;

R_1 is selected from the group consisting of: hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, alkanoyl, alkanoyloxy, alkoxycarbonyl, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylthio, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, and in the case of aryl, methylenedioxy;

R_6 is selected from the group consisting of =O and =S;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

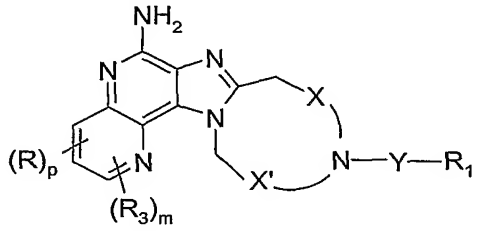
R_9 is selected from the group consisting of hydrogen and alkyl;

R_{11} is selected from the group consisting of C_{1-6} alkyl and $-Si(C_{1-6}\ alkyl)_3$; and

n is an integer from 0 to 4;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a compound of Formula VI:



VI

wherein:

X is a bond or a straight or branched chain C_{1-2} alkylene;

X' is a straight or branched chain C_{1-8} alkylene optionally substituted with hydroxy, $-O-R_{11}$, or one or more halogen atoms wherein the hydroxy, $-O-R_{11}$, or one or more

halogen atoms are bonded to a carbon atom other than a carbon atom adjacent to a nitrogen atom;

X and X' are further characterized in that the total number of ring carbon atoms contributed by X and X' is 1 to 3;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-C(R_6)-N(R_8)-$,

$-C(R_6)-N(R_8)-C(R_6)-$, and

$-C(R_6)-N(R_8)-S(O)_2-$;

R_1 is selected from the group consisting of: hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, alkanoyl, alkanoyloxy, alkoxycarbonyl, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylthio, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, and in the case of aryl, methylenedioxy;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_3 is selected from the group consisting of:

$-Z-R_4$,

$-Z-X''-R_4$,

$-Z-X''-Y'-R_4$,

$-Z-X''-Y'-X''-Y'-R_4$, and

$-Z-X''-R_5$;

X'' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y' is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

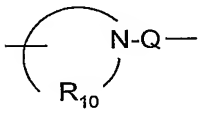
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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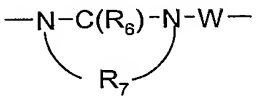

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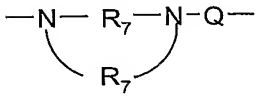

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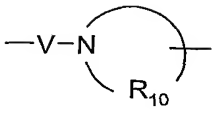
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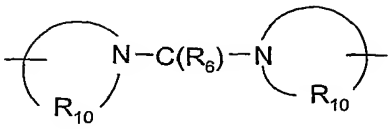
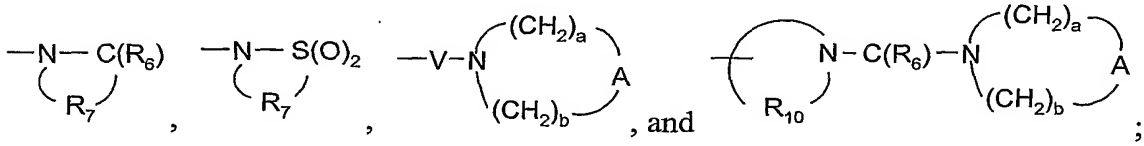

;

Z is a bond or -O-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of


;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

R_{11} is selected from the group consisting of C_{1-6} alkyl and $-Si(C_{1-6}\ alkyl)_3$;

A is selected from the group consisting of $-CH_2$-, -O-, -C(O)-, $-S(O)_{0-2}$-, and $-N(R_4)$-;

Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(R_6)-O-, and -C(R_6)-N(OR_9);

V is selected from the group consisting of -C(R_6)-, -O-C(R_6)-, -N(R_8)-C(R_6)-, and -S(O)$_2$-;

W is selected from the group consisting of a bond, -C(O)-, and –S(O)$_2$-;

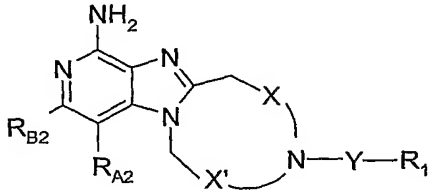
m is 0 or 1; with the proviso that when m is 1, then p is 0 or 1;

p is an integer from 0 to 3; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a compound of Formula VII:



VII

wherein:

R_{A2} and R_{B2} are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

X is a bond or a straight or branched chain C_{1-2} alkylene;

X' is a straight or branched chain C_{1-8} alkylene optionally substituted with hydroxy, -O-R_{11}, or one or more halogen atoms wherein the hydroxy, -O-R_{11}, or one or more halogen atoms are bonded to a carbon atom other than a carbon atom adjacent to a nitrogen atom;

X and X' are further characterized in that the total number of ring carbon atoms contributed by X and X' is 1 to 3;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-C(R_6)-N(R_8)-$,

$-C(R_6)-N(R_8)-C(R_6)-$, and

$-C(R_6)-N(R_8)-S(O)_2-$;

R_1 is selected from the group consisting of: hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, alkanoyl, alkanoyloxy, alkoxycarbonyl, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylthio, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, and in the case of aryl, methylenedioxy;

R_6 is selected from the group consisting of =O and =S;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl; and

R_{11} is selected from the group consisting of C_{1-6} alkyl and $-Si(C_{1-6}$ alkyl$)_3$;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides 9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine or a pharmaceutically acceptable salt thereof.

As used herein, the terms "alkyl," "alkenyl," "alkynyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, i.e. cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms, and alkynyl groups containing from 2 to 20 carbon atoms. In some embodiments, these groups have a total of up to 10 carbon atoms, up to 8 carbon atoms, up to 6 carbon atoms, or up to 4 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopropylmethyl, cyclopentyl, cyclohexyl, adamantyl, and substituted and unsubstituted bornyl, norbornyl, and norbornenyl.

Unless otherwise specified, "alkylene," "alkenylene," and "alkynylene" are the divalent forms of the "alkyl," "alkenyl," and "alkynyl" groups defined above. The terms, "alkylenyl," "alkenylenyl," and "alkynylenyl" are use when "alkylene," "alkenylene," and "alkynylene," respectively, are substituted. For example, an arylalkylenyl group comprises an alkylene moiety to which an aryl group is attached.

The term "haloalkyl" is inclusive of groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of other groups that include the prefix "halo-." Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like.

The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl.

Unless otherwise indicated, the term "heteroatom" refers to the atoms O, S, or N.

The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N). Suitable heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxalinyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, pyrazinyl, 1-oxidopyridyl, pyridazinyl, triazinyl, tetrazinyl, oxadiazolyl, thiadiazolyl, and so on.

The term "heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. Exemplary

heterocyclic groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, tetrahydropyranyl, quinuclidinyl, homopiperidinyl (azepanyl), homopiperazinyl (diazepanyl), 1,3-dioxolanyl, aziridinyl, dihydroisoquinolin-(1*H*)-yl, octahydroisoquinolin-(1*H*)-yl, dihydroquinolin-(2*H*)-yl, octahydroquinolin-(2*H*)-yl, dihydro-1*H*-imidazolyl, and the like. When "heterocyclyl" contains a nitrogen atom, the point of attachment of the heterocyclyl group may be the nitrogen atom.

The terms "arylene," "heteroarylene," and "heterocyclylene" are the divalent forms of the "aryl," "heteroaryl," and "heterocyclyl" groups defined above. The terms, "arylenyl," "heteroarylenyl," and "heterocyclylenyl" are used when "arylene," "heteroarylene," and "heterocyclylene," respectively, are substituted. For example, an alkylarylenyl group comprises an arylene moiety to which an alkyl group is attached.

Herein, "non-interfering" means that the ability of the compound or salt, which includes a non-interfering substituent, to modulate the biosynthesis of one or more cytokines is not destroyed by the non-interfering substitutent. For certain embodiments, R' is a non-interfering substituent. Illustrative R' groups include those described herein for R and R_3.

When a group (or substituent or variable) is present more than once in any Formula described herein, each group (or substituent or variable) is independently selected, whether explicitly stated or not. For example, for the formula $-N(R_9)_2$ each R_9 group is independently selected. In another example, when a Y and a Y' group both contain an R_8 group, each R_8 group is independently selected. In a further example, when more than one Y' group is present (i.e., -Z-X"-Y'-X"-Y'-R_4) and each Y' group contains one or more R_6 groups, then each Y' group is independently selected, and each R_6 group is independently selected.

The invention is inclusive of the compounds described herein in any of their pharmaceutically acceptable forms, including isomers (e.g., diastereomers and enantiomers), salts, solvates, polymorphs, and the like. In particular, if a compound is optically active, the invention specifically includes each of the compound's enantiomers as well as racemic mixtures of the enantiomers. It should be understood that the term "compound" includes any or all of such forms, whether explicitly stated or not (although at times, "salts" are explicitly stated).

For any of the compounds presented herein, each one of the following variables (e.g., R_1, R_3, R, R', R_A, R_B, R_{A1}, R_{B1}, R_{A2}, R_{B2}, A, V, X, X', Y, m, n, and p and so on) in any of its embodiments can be combined with any one or more of the other variables in any of their embodiments and associated with any one of the formulas described herein, as would be understood by one of skill in the art. Each of the resulting combinations of variables is an embodiment of the present invention.

In some embodiments, compounds of Formulas I-VII induce the biosynthesis of one or more cytokines.

In some embodiments, compounds of Formulas I-VII inhibit the biosynthesis of one or more cytokines (e.g., TNF-α).

In certain embodiments, compounds of Formulas I-VII induce the biosynthesis of one or more cytokines and inhibit the biosynthesis of one or more cytokines (e.g., TNF-α).

For certain embodiments, R_A and R_B are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$; or when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R' groups; or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups.

For certain embodiments, R_A and R_B are each independently selected from the group consisting of: hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$.

For certain embodiments, when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R' groups.

For certain embodiments, when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups.

For certain embodiments, R_{A1} and R_{B1} are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$; or when taken together, R_{A1} and R_{B1} form a fused aryl ring or heteroaryl ring containing one

heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group; or when taken together, R_{A1} and R_{B1} form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups.

For certain embodiments, R_{A1} and R_{B1} are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$.

For certain embodiments, when taken together, R_{A1} and R_{B1} form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group.

For certain embodiments, when taken together, R_{A1} and R_{B1} form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups.

In some embodiments of Formula II, R_{A1} and R_{B1} form a fused benzene ring which is unsubstituted.

In some embodiments of Formula II, R_{A1} and R_{B1} form a fused pyridine ring which is unsubstituted.

In some embodiments of Formula II, R_{A1} and R_{B1} form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, wherein the ring is unsubstituted.

For certain embodiments, R_{A2} is selected from the group consisting of: hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$.

For certain embodiments, R_{B2} is selected from the group consisting of: hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$.

For certain embodiments, R_{A2} and R_{B2} are each methyl.

For certain embodiments, X is a bond or a straight or branched chain C_{1-2} alkylene. For certain embodiments, X is a bond.

For certain embodiments, X' is a straight or branched chain C_{1-8} alkylene optionally substituted with hydroxy, $-O-R_{11}$, or one or more halogen atoms wherein the hydroxy, $-O-R_{11}$, or one or more halogen atoms are bonded to a carbon atom other than a

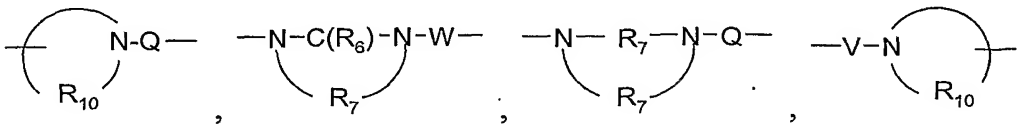
carbon atom adjacent to a nitrogen atom. For certain embodiments, particularly embodiments of Formulas III and IV, X' is a straight or branched chain C_{1-8} alkylene optionally substituted with hydroxy wherein the hydroxy is bonded to a carbon atom other than a carbon atom adjacent a nitrogen atom. For certain embodiments, X' is methylene. For certain embodiments, X' is ethylene. For certain embodiments, X' is $-CF_2-CH_2-$.

For certain embodiments, X and X' are further characterized in that the total number of ring carbon atoms contributed by X and X' is 1 to 3. For certain embodiments, the total number of ring carbon atoms contributed by X and X' is 1. For certain embodiments, the total number of ring carbon atoms contributed by X and X' is 2. For certain embodiments, X' contributes one ring carbon atom. For certain embodiments, X' contributes two ring carbon atoms.

For certain embodiments, X" is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups. For certain embodiments, X" is propylene. For certain embodiments, X" is methylene.

For certain embodiments, Y is selected from the group consisting of a bond, $-S(O)_2-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-C(R_6)-N(R_8)-$, $-C(R_6)-N(R_8)-C(R_6)-$, and $-C(R_6)-N(R_8)-S(O)_2-$. For certain embodiments, particularly embodiments of Formulas III and IV, Y is selected from the group consisting of a bond, $-S(O)_2-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-N(R_8)-$, $-C(R_6)-N(R_8)-C(R_6)-$, and $-C(R_6)-N(R_8)-S(O)_2-$. For certain embodiments, Y is selected from the group consisting of $-C(O)-$, $-S(O)_2-$, or $-C(O)-NH-$. For certain embodiments, Y is $-S(O)_2-$.

For certain embodiments, Y' is selected from the group consisting of $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, $-O-C(O)-O-$, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, $-C(R_6)-N(OR_9)-$,



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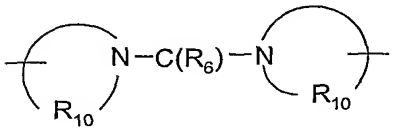

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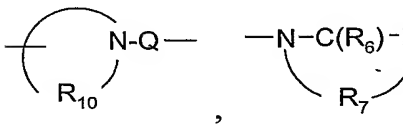
For certain embodiments, Y' is selected from the group consisting of -S(O)$_{0-2}$-, -S(O)$_2$-N(R$_8$)-, -C(R$_6$)-, -C(R$_6$)-O-, -O-C(R$_6$)-, -O-C(O)-O-, -N(R$_8$)-Q-, -C(R$_6$)-N(R$_8$)-, -O-C(R$_6$)-N(R$_8$)-, -C(R$_6$)-N(OR$_9$)-,



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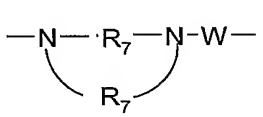

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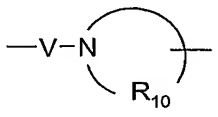

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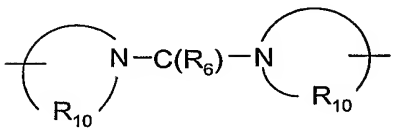

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For certain embodiments, Z is a bond or -O-. For certain embodiments, Z is a bond. For certain embodiments, Z is -O-.

For certain embodiments, R is selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, alkylthio, and -N(R$_9$)$_2$. For certain embodiments, R is hydroxy. For certain embodiments, R is halogen. For certain embodiments, R is fluoro. For certain embodiments, R is a substituent at the 2-position. For certain embodiments, R is a substituent at the 3-position.

For certain embodiments, R$_1$ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, alkanoyl, alkanoyloxy, alkoxycarbonyl, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylthio, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, and in the case of aryl, methylenedioxy.

For certain embodiments, R$_1$ is not hydrogen or C$_{1-4}$ alkyl. For example, for certain embodiments of Formula I, when R$_A$ and R$_B$ together form a fused benzene ring that is unsubstituted or substituted by C$_{1-4}$ alkyl, C$_{1-4}$ alkoxy, or halogen, and Y is a bond, R$_1$ is not hydrogen or C$_{1-4}$ alkyl. For certain embodiments of Formula II, when R$_{A1}$ and

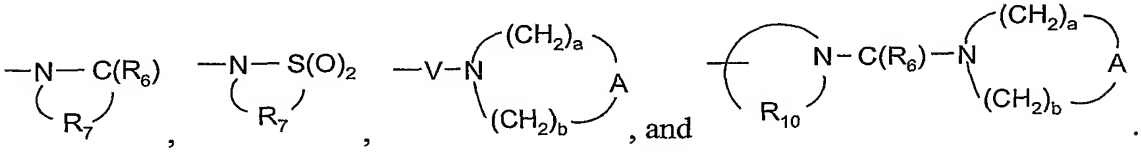
R_{B1} together form a fused benzene ring that is unsubstituted or substituted by C_{1-4} alkyl, C_{1-4} alkoxy, or halogen, and Y is a bond, R_1 is not hydrogen or C_{1-4} alkyl. For certain embodiments of Formula IV, R_1 is not hydrogen or C_{1-4} alkyl when Y is a bond, and either n and m are both 0, or m is 0, n is 1, and R is selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, and halogen. For certain embodiments, particularly embodiments of Formulas III and IV, when Y is a bond, R_1 is not hydrogen or C_{1-4} alkyl.

For certain embodiments, R_1 is C_{1-3} alkyl. For certain embodiments, R_1 is methyl. For certain embodiments, R_1 is trifluoromethyl.

For certain embodiments, R_3 is selected from the group consisting of: -Z-R_4, -Z-X"-R_4, -Z-X"-Y'-R_4, -Z-X"-Y'-X"-Y'-R_4, and -Z-X"-R_5. For certain embodiments, R_3 is pyridyl, benzyloxy, or 3-pyrrolylpropoxy. For certain embodiments, R_3 is at the 2-position. For certain embodiments, R_3 is at the 3-position.

For certain embodiments, R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo. For certain embodiments, R_4 is aryl or heteroaryl.

For certain embodiments, R_5 is selected from the group consisting of



, , , and .

For certain embodiments, R_6 is selected from the group consisting of =O and =S. For certain embodiments, R_6 is =O.

For certain embodiments, R_7 is C_{2-7} alkylene.

For certain embodiments, R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl.

For certain embodiments, R_9 is selected from the group consisting of hydrogen and alkyl.

For certain embodiments, R_{10} is C_{3-8} alkylene.

For certain embodiments, R_{11} is selected from the group consisting of C_{1-6} alkyl and $-Si(C_{1-6}\ alkyl)_3$. For certain embodiments, R_{11} is $-Si(C_{1-6}\ alkyl)_3$. For certain embodiments, R_{11} is a *tert*-butyldimethylsilanyl group.

For certain embodiments, R' is a non-interfering substituent. Herein, "non-interfering" means that the immunomodulator activity (for example, the ability to induce the biosynthesis of one or more cytokines or the ability to inhibit the biosynthesis of one or more cytokines) of the compound having a non-interfering substituent is not destroyed. Illustrative R' groups include those described herein for R and R_3.

For certain embodiments, A is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$.

For certain embodiments, Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)$.

For certain embodiments, V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$.

For certain embodiments, W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$.

For certain embodiments, a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7. For certain embodiments, a and b are each 2.

For certain embodiments, m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1. For certain embodiments, m is 0 or 1; with the proviso that when m is 1, then p is 0 or 1. For certain embodiments, m is 0. For certain embodiments, m is 1.

For certain embodiments, n is an integer from 0 to 4. For certain embodiments, n is 0. For certain embodiments, n is 1.

For certain embodiments, p is an integer from 0 to 3. For certain embodiments, p is 0.

For certain embodiments, particularly embodiments of Formulas III and IV, X is a bond and X' contributes one ring carbon atom. For certain embodiments, particularly

embodiments of Formulas III and IV, X is a bond and X' contributes two ring carbon atoms.

For certain embodiments, Y is selected from the group consisting of -C(O)-, $-S(O)_2-$, or –C(O)-NH-, and R_1 is C_{1-3} alkyl. For certain embodiments, particularly embodiments of Formulas III and IV, Y is $-S(O)_2-$ and R_1 is methyl. For certain embodiments, Y is $-S(O)_2-$ and R_1 is trifluoromethyl.

For certain embodiments, particularly embodiments of Formulas III and IV, m and n are 0.

For certain embodiments, particularly embodiments of Formulas III and IV, R_1 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, alkanoyl, alkanoyloxy, alkoxycarbonyl, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylthio, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, and in the case of aryl, methylenedioxy; further with the proviso that when Y is a bond, R_1 is not hydrogen or C_{1-4} alkyl.

In one embodiment, the present invention provides 9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine or a pharmaceutically acceptable salt thereof.

Preparation of the Compounds

Compounds of the invention can be prepared according to Reaction Scheme I, wherein R, R_1, X, X', Y, and n are as defined above, Hal is chloro, bromo, or iodo, and Boc is *tert*-butoxycarbonyl. Reaction Scheme I shows two routes to a 1*H*-imidazoquinolin-6-amine of Formula XVI; the routes are labeled Ia and Ib. In step (1) of Reaction Scheme I, a quinoline-3,4-diamine of Formula X is reacted with a carboxylic

acid equivalent, which is selected such that it will provide the desired -X-Hal substituent in a 1*H*-imidazoquinoline of Formula XI. When the carboxylic acid equivalent is an acid halide of formula Hal-CH_2-X-C(O)Cl or Hal-CH_2-X-C(O)Br, the reaction is conveniently carried out by adding the acid halide to a solution of a quinoline-3,4-diamine of Formula X in a suitable solvent such as dichloromethane or 1,2-dichloroethane in the presence of a tertiary amine such as triethylamine. The reaction can be carried out at ambient temperature or at an elevated temperature. The product can be isolated by conventional methods.

The reaction with an acid halide of formula Hal-CH_2-X-C(O)Cl or Hal-CH_2-X-C(O)Br may be carried out in two parts, which include (i) adding the acid halide to a solution of a quinoline-3,4-diamine of Formula X in a suitable solvent such as dichloromethane or 1,2-dichloroethane optionally in the presence of a tertiary amine such as triethylamine to afford an amide intermediate and (ii) cyclizing to provide a 1*H*-imidazoquinoline of Formula XI. The amide intermediate from part (i) can be optionally isolated using conventional techniques. The cyclization in part (ii) may be carried out by heating the amide intermediate from part (i) in a suitable solvent such as toluene to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula XI. The cyclization in part (ii) can also be carried out in the presence of a base such as triethylamine.

Some compounds of Formula X are known; others can be made by known routes. See, for example, U.S. Patent Nos. 6,331,539 (Crooks et al.), 6,451,485 (Crooks et al.), 6,451,810 (Coleman et al.), and 6,677,349 (Griesgraber).

In step (2) of Reaction Scheme I, a 1*H*-imidazoquinoline of Formula XI is cyclized by an intramolecular displacement of the halogen by the carbamate-protected amino group. The reaction is conveniently carried out by adding a base such as potassium *tert*-butoxide to a solution of a 1*H*-imidazoquinoline of Formula XI in a suitable solvent such as tetrahydrofuran. The reaction can be carried out at ambient temperature or at a sub-ambient temperature such as 0 °C. The product can be isolated using conventional methods.

In step (3a) of Reaction Scheme I, a 1*H*-imidazo[4,5-*c*]quinoline of Formula XII is oxidized to provide a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XIII using a conventional oxidizing agent capable of forming *N*-oxides. The reaction is conveniently carried out by adding 3-chloroperoxybenzoic acid to a solution of a compound of Formula

XII in a solvent such as chloroform or dichloromethane. The reaction can be carried out at ambient temperature. The product can be isolated using conventional methods.

In step (4a) of Reaction Scheme I, a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XIII is aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XIV. Step (4a) involves the activation of an *N*-oxide of Formula XIII by conversion to an ester and then reacting the ester with an aminating agent. Suitable activating agents include alkyl- or arylsulfonyl chlorides such as benzenesulfonyl chloride, methanesulfonyl chloride, or *p*-toluenesulfonyl chloride. Suitable aminating agents include ammonia, in the form of ammonium hydroxide, for example, and ammonium salts such as ammonium carbonate, ammonium bicarbonate, and ammonium phosphate. The reaction is conveniently carried out by adding ammonium hydroxide to a solution of the *N*-oxide of Formula XIII in a suitable solvent such as dichloromethane or chloroform and then adding *p*-toluenesulfonyl chloride. The reaction can be carried out at ambient temperature, and the product can be isolated from the reaction mixture using conventional methods.

In step (5a) of Reaction Scheme I, the Boc protecting group of a 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XIV is removed under acidic conditions to provide a 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XV. The deprotection is conveniently carried out by adding a solution of hydrogen chloride in 1,4-dioxane or a solution of trifluoroacetic acid in dichloromethane to the 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XIV. The reaction may be run in a suitable solvent such as dichloromethane. The reaction can be carried out at ambient temperature, and the product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (6a) of Reaction Scheme I, the secondary amine of the 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XV or a salt thereof is converted to an amide, sulfonamide, sulfamide, urea, or tertiary amine of Formula XVI using conventional methods. Formula XVI represents a subgenus of Formulas I, II, III, and IV. In step (6a), a 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XV or a salt thereof can react with an acid chloride of Formula $R_1C(O)Cl$ to provide a compound of Formula XVI in which Y is -C(O)-. In addition, a 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XV can react with sulfonyl chloride of Formula $R_1S(O)_2Cl$ or a sulfonic anhydride of Formula $(R_1S(O)_2)_2O$ to provide a compound of Formula XVI in which Y is $-S(O)_2-$. Numerous acid chlorides of Formula $R_1C(O)Cl$, sulfonyl chlorides of Formula $R_1S(O)_2Cl$, and sulfonic anhydrides of Formula

$(R_1S(O)_2)_2O$ are commercially available; others can be readily prepared using known synthetic methods. The reaction is conveniently carried out by adding the acid chloride of Formula $R_1C(O)Cl$, sulfonyl chloride of Formula $R_1S(O)_2Cl$, or sulfonic anhydride of Formula $(R_1S(O)_2)_2O$ to a solution of the compound of Formula XV in a suitable solvent such as chloroform, dichloromethane, or *N,N*-dimethylformamide (DMF). Optionally a base such as triethylamine or *N,N*-diisopropylethylamine can be added. The reaction can be carried out at ambient temperature or a sub-ambient temperature such as 0 °C. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Ureas of Formula XVI, where Y is $-C(O)-N(R_8)-$ and R_8 is defined as above, can be prepared by reacting a 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XV or a salt thereof with isocyanates of Formula $R_1N=C=O$. Numerous isocyanates of Formula $R_1N=C=O$ are commercially available; others can be readily prepared using known synthetic methods. The reaction can be conveniently carried out by adding the isocyanate of Formula $R_1N=C=O$ to a solution of the 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XV in a suitable solvent such as DMF or chloroform. Optionally a base such as triethylamine or *N,N*-diisopropylethylamine can be added. The reaction can be carried out at ambient temperature or a sub-ambient temperature such as 0 °C. Alternatively, a compound of Formula XV can be treated with an isocyanate of Formula $R_1(CO)N=C=O$, a thioisocyanate of Formula $R_1N=C=S$, a sulfonyl isocyanate of Formula $R_1S(O)_2N=C=O$, or a carbamoyl chloride of Formula $R_1N-(R_8)-C(O)Cl$ to provide a compound of Formula XVI, where Y is $-C(O)-N(R_8)-(CO)-$, $-C(S)-N(R_8)-$, $-C(O)-N(R_8)-S(O)_2-$, or $-C(O)-N(R_8)-$, respectively. Alternatively, a compound of Formula XV can be treated with a carbamoyl chloride of Formula Cl-C(O)-heterocyclyl, wherein heterocyclyl is attached at nitrogen atom, to provide a compound of Formula XVI, wherein Y is -C(O)- and R_1 is heterocyclyl attached at the nitrogen atom. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Sulfamides of Formula XVI, where Y is $-S(O)_2-N(R_8)-$, can be prepared by reacting a compound or salt of Formula XV with sulfuryl chloride to generate a sulfamoyl chloride in situ, and then reacting the sulfamoyl chloride with an amine of formula $HN(R_8)R_1$. Alternatively, sulfamides of Formula XVI can be prepared by reacting a compound of Formula XV with a sulfamoyl chloride of formula $R_1(R_8)N-S(O)_2Cl$. The

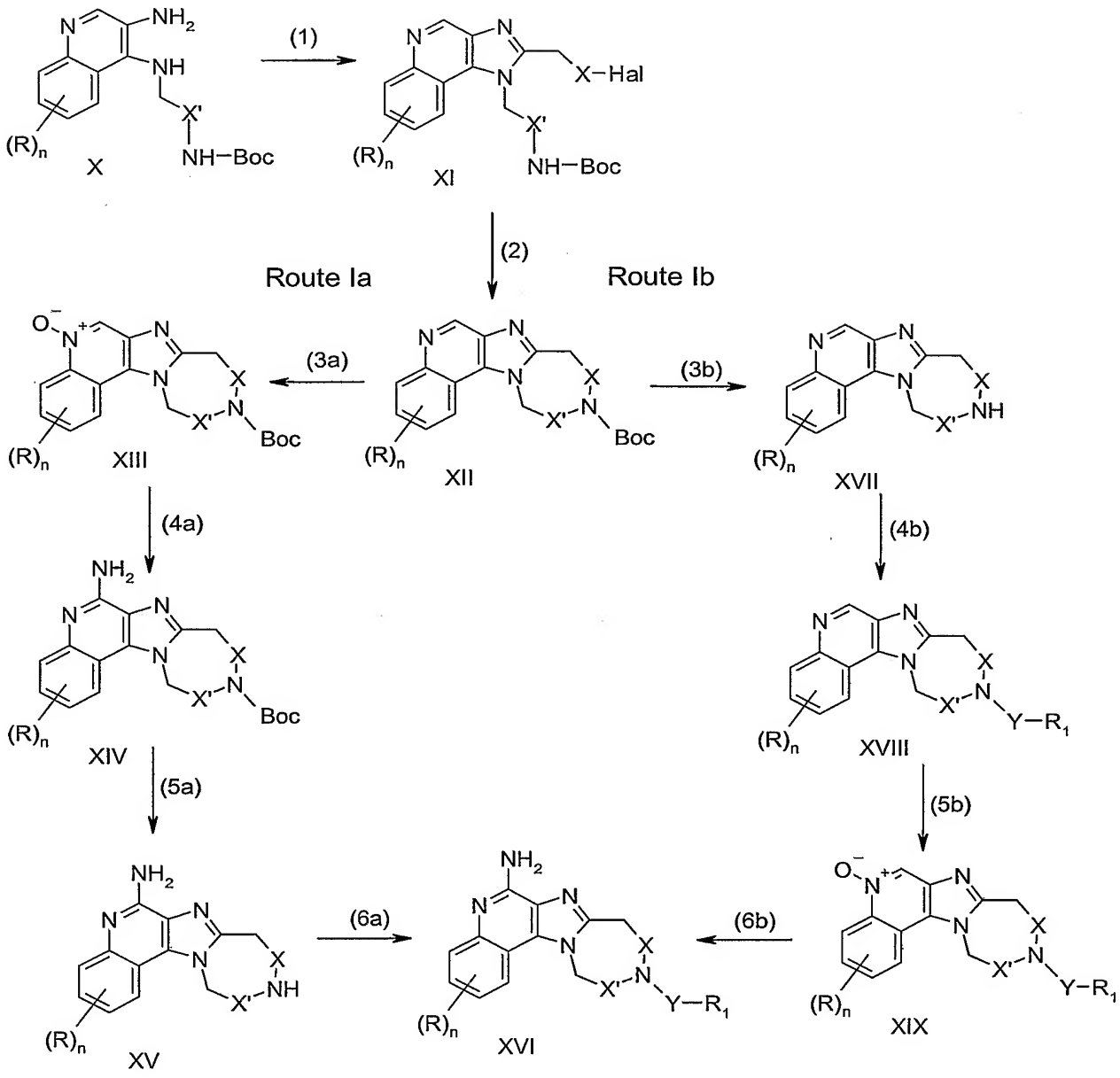
product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods. Many sulfonyl chlorides of Formula $R_1S(O)_2Cl$ and amines of Formula $HN(R_8)R_1$, and some sulfamoyl chlorides of formula $R_1(R_8)N\text{-}S(O)_2Cl$ are commercially available; others can be prepared using known synthetic methods.

Compounds of Formula XVI where Y is a bond can be prepared by reductive alkylation of the secondary amine of the 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XV. The alkylation is conveniently carried out in two parts by (i) adding an aldehyde or ketone to a solution of a 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XV or a salt thereof in a suitable solvent such as DMF in the presence of a base such as *N,N*-diisopropylethylamine. In part (ii) the reduction is carried out by adding a suitable reducing agent such as the borane-pyridine complex. Both part (i) and part (ii) can be carried out at ambient temperature, and the product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In steps (3b) and (4b) of Route Ib of Reaction Scheme I, the Boc protecting group of a 1*H*-imidazo[4,5-*c*]quinoline of Formula XII is first removed to product a 1*H*-imidazo[4,5-*c*]quinoline of Formula XVII or a pharmaceutically acceptable salt thereof, which is then converted to an amide, sulfonamide, urea, sulfamide, or tertiary amine of Formula XIII. Steps (3b) and (4b) of Route Ib can be carried out as described in steps (5a) and (6a) of Route Ia of Reaction Scheme I.

In steps (5b) and (6b) of Route Ib of Reaction Scheme I, a compound of Formula XVIII is first oxidized to a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XIX, which is then aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XVI. Steps (5b) and (6b) of Route Ib can be carried out as described in steps (3a) and (4a) of Route Ia of Reaction Scheme I. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme I



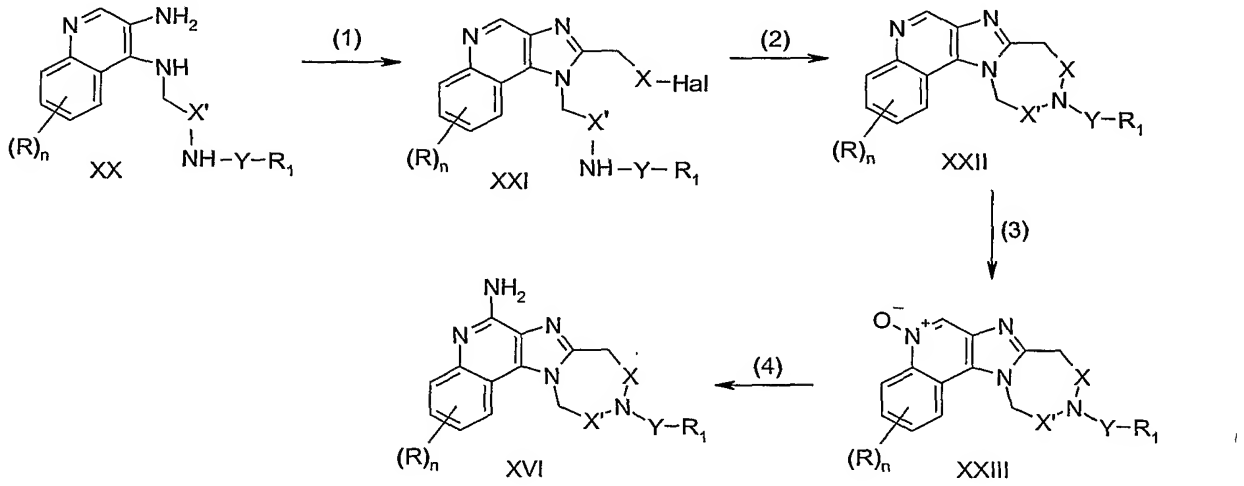
Compounds of the invention can also be prepared according to Reaction Scheme II, wherein R, R_1, X, X', Y, and n are as defined above and Hal is chloro, bromo, or iodo. In step (1) of Reaction Scheme II, a quinoline-3,4-diamine of Formula XX is reacted with an acid halide of formula Hal-CH_2-X-C(O)Cl or Hal-CH_2-X-C(O)Br to provide a 1*H*-imidazoquinoline of Formula XXI. The reaction is conveniently carried out as described for step (1a) of Reaction Scheme I.

Compounds of Formula XX are known or can be readily prepared using known synthetic routes; see for example, U.S. Patent Nos. 4,689,338 (Gerster), 5,268,376 (Gerster), 6,331,539 (Crooks et al.), 6,451,810 (Coleman et al.), 6,541,485 (Crooks et al.).

In step (2) of Reaction Scheme II, a 1*H*-imidazoquinoline of Formula XXI is cyclized by an intramolecular displacement of the halogen by the carbamate-protected amino group. The reaction is conveniently carried out as described in step (2) of Reaction Scheme I to provide a compound of Formula XXII. Steps (1) and (2) may be effected in one step if the reaction in step (1) is heated at reflux for a day or two in a suitable solvent such as 1,2-dichloroethane.

In steps (3) and (4) of Reaction Scheme II, a compound of Formula XXII is first oxidized to a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XXIII, which is then aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XVI. Steps (3) and (4) of Reaction Scheme II can be carried out as described in steps (3a) and (4a) of Route Ia of Reaction Scheme I. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme II



For some embodiments, compounds of the invention are prepared according to Reaction Scheme III, wherein R, R_1, X, X', Y, n, and Boc are as defined above; each Hal is independently chloro, bromo, or iodo; R_{3a} is -Z-R_{4b}, -Z-X"$_a$-R_4, -Z-X"$_b$-Y'-R_4, and

-Z-X"$_b$-R_5; where Z is a bond; X"$_a$ is alkenylene; X"$_b$ is arylene, heteroarylene, and alkenylene interrupted or terminated by arylene or heteroarylene; R_{4b} is aryl or heteroaryl where the aryl or heteroaryl groups can be unsubstituted or substituted as defined in R_4 above; and R_4, R_5, and Y' are as defined above. In step (1) of Reaction Scheme III, a quinoline-3,4-diamine of Formula XXIV is reacted with an acid halide of formula Hal-CH_2-X-C(O)Cl or Hal-CH_2-X-C(O)Br to provide a 1*H*-imidazoquinoline of Formula XXV. The reaction can be carried out as described in step (1) of Reaction Scheme I.

Compounds of Formula XXIV are known or can be readily prepared using known synthetic routes. See, for example, U.S. Patent Nos. 6,331,539 (Crooks et al.), 6,451,485 (Crooks et al.), 6,451,810 (Coleman et al.), and 6,677,349 (Griesgraber) and U.S. Patent Publication Application No. US 2004/0147543.

In step (2) of Reaction Scheme III, a 1*H*-imidazoquinoline of Formula XXV is cyclized by an intramolecular displacement of the halogen by the carbamate-protected amino group. The reaction can be carried out as described in step (2) of Reaction Scheme I to provide a compound of Formula XXVI.

In steps (3) and (4) of Reaction Scheme III, a compound of Formula XXVI is first oxidized to a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XXVII, which is then aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XXVIII. Steps (3) and (4) of Reaction Scheme III can be carried out as described in steps (3a) and (4a) of Route Ia of Reaction Scheme I.

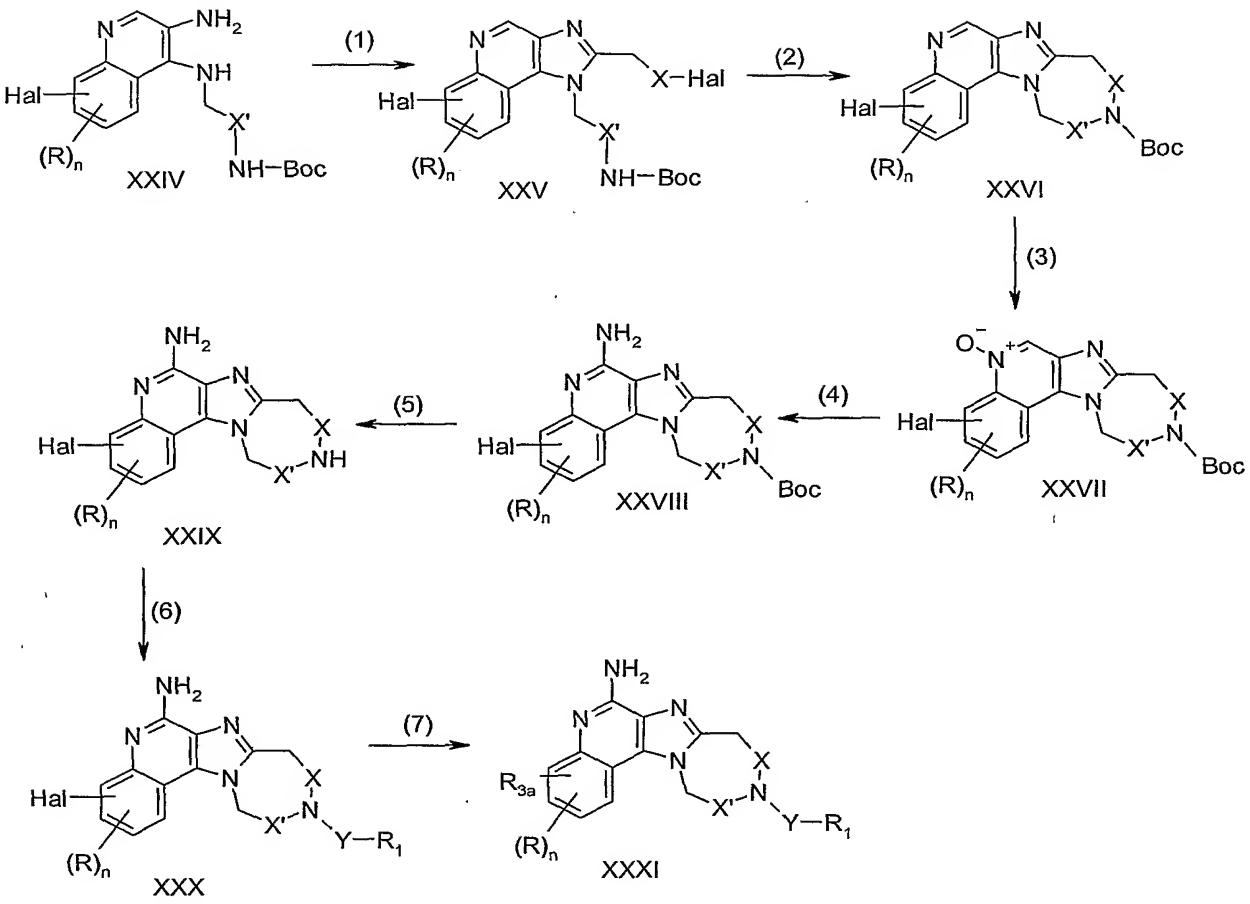
In steps (5) and (6) of Reaction Scheme III, the Boc protecting group of a 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XXVIII is first removed to provide a 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XXIX or a pharmaceutically acceptable salt thereof. The compound of Formula XXIX is then converted to an amide, sulfonamide, urea, or sulfamide of Formula XXX in step (6). Steps (5) and (6) of Reaction Scheme III can be carried out as described in steps (5a) and (6a) of Route Ia of Reaction Scheme I.

In step (7) of Reaction Scheme III, a 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XXX is coupled with a boronic acid of Formula R_{3a}-B(OH)$_2$, an anhydride thereof, or a boronic acid ester of Formula R_{3a}-B(O-alkyl)$_2$ to provide an 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XXXI, which is a subgenus of Formulas I, II, III, and IV. The Suzuki coupling is carried out by combining a compound of Formula XXX with a boronic acid or an ester or anhydride thereof in the presence of palladium (II) acetate,

triphenylphosphine, and a base such as sodium carbonate in a suitable solvent such as *n*-propanol or solvent mixture such as *n*-propanol/water. The reaction can be carried out at an elevated temperature (e.g., 80-100°C). Many boronic acids of Formula R_{3a}-$B(OH)_2$, anhydrides thereof, and boronic acid esters of Formula R_{3a}-B(O-alkyl)$_2$ are commercially available; others can be readily prepared using known synthetic methods. See, for example, Li, W. et al, *J. Org. Chem.*, *67*, 5394-5397 (2002). The product of Formula XXXI or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Other coupling reactions such as the Heck reaction, the Stille coupling, and the Sonogashira coupling can be used to prepare compounds of Formula XXXI. Also, compounds of Formula XXXI, wherein R_{3a} is -Z-X"$_a$-R_4, -Z-X"$_b$-Y'-R_4, and -Z-X"$_b$-R_5 in which X"$_b$ is alkenylene interrupted or terminated by arylene or heteroarylene, can undergo reduction of the X"$_a$ or X"$_b$ alkenylene group. The reduction can be carried out by hydrogenation using a conventional heterogeneous hydrogenation catalyst such as palladium on carbon. The reaction can conveniently be carried out on a Parr apparatus in a suitable solvent such as ethanol, methanol, or mixtures thereof. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme III



Compounds of the invention can be prepared according to Reaction Scheme IV where R, R_1, X, X', Y, n, and Boc are as defined above; R_{3b} is -Z-R_4, -Z-X"-R_4, -Z-X"-Y'-R_4, -Z-X"-Y'-X"-Y'-R_4, or -Z-X"-R_5, where R_4, X", Y', and R_5 are as defined above; and Z is -O-. In step (1) of Reaction Scheme IV, a benzyloxyaniline of Formula XXXII is treated with the condensation product generated from 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) and triethyl orthoformate to provide an imine of Formula XXXIII. The reaction is conveniently carried out by adding a solution of a benzyloxyaniline of Formula XXXII to a heated mixture of Meldrum's acid and triethyl orthoformate and heating the reaction at an elevated temperature such as 45 °C. The product can be isolated using conventional methods.

In step (2) of Reaction Scheme IV, an imine of Formula XXXIII undergoes thermolysis and cyclization to provide a benzyloxyquinolin-4-ol of Formula XXXIV. The

reaction is conveniently carried out in a heat transfer fluid such as DOWTHERM A heat transfer fluid at a temperature between 200 and 250 °C. The product can be isolated using conventional methods.

In step (3) of Reaction Scheme IV, the benzyloxyquinolin-4-ol of Formula XXXIV is nitrated under conventional nitration conditions to provide a benzyloxy-3-nitroquinolin-4-ol of Formula XXXV. The reaction is conveniently carried out by adding nitric acid to the benzyloxyquinolin-4-ol of Formula XXXIV in a suitable solvent such as propionic acid and heating the mixture at an elevated temperature such as 125 °C. The product can be isolated using conventional methods.

In step (4) of Reaction Scheme IV, a benzyloxy-3-nitroquinolin-4-ol of Formula XXXV is chlorinated using conventional chlorination chemistry to provide a benzyloxy-4-chloro-3-nitroquinoline of Formula XXXVI. The reaction is conveniently carried out by treating the benzyloxy-3-nitroquinolin-4-ol of Formula XXXV with phosphorous oxychloride in a suitable solvent such as DMF. The reaction can be carried out at an elevated temperature such as 100 °C, and the product can be isolated using conventional methods.

In step (5) of Reaction Scheme IV, a benzyloxy-4-chloro-3-nitroquinoline of Formula XXXVI is treated with an amine of Formula Boc-NH-X'-CH_2-NH_2 to provide a benzyloxy-3-nitroquinolin-4-amine of Formula XXXVII. Several amines of Formula Boc-NH-X'-CH_2-NH_2 are commercially available; others can be prepared by known synthetic methods. The reaction is conveniently carried out by adding the amine of Formula Boc-NH-X'-CH_2-NH_2 to a solution of the benzyloxy-4-chloro-3-nitroquinoline of Formula XXXVI in a suitable solvent such as dichloromethane or methanol in the presence of a tertiary amine such as triethylamine. The reaction can be carried out at ambient temperature or at an elevated temperature such as, for example, the reflux temperature of the solvent. The reaction product can be isolated using conventional methods.

In step (6) of Reaction Scheme IV, a benzyloxy-3-nitroquinolin-4-amine of Formula XXXVI is reduced to provide a benzyloxyquinoline-3,4-diamine of Formula XXXVIII. The reaction can be carried out by hydrogenation using a heterogeneous hydrogenation catalyst such as platinum on carbon. The hydrogenation is conveniently carried out in a Parr apparatus in a suitable solvent such as toluene, methanol, or

acetonitrile. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods.

Alternatively, the reduction in step (6) can be carried out using nickel boride, prepared *in situ* from sodium borohydride and nickel(II) chloride. The reduction is conveniently carried out by adding a solution of the benzyloxy-3-nitroquinolin-4-amine of Formula XXXVII in a suitable solvent or solvent mixture such as dichloromethane/methanol to a mixture of excess sodium borohydride and catalytic nickel(II) chloride in methanol. The reaction can be carried out at ambient temperature. The product can be isolated using conventional methods.

In step (7) of Reaction Scheme IV, a benzyloxyquinoline-3,4-diamine of Formula XXXVIII is treated with an acid halide of formula Hal-CH_2-X-C(O)Cl or Hal-CH_2-X-C(O)Br to provide a benzyloxy-1*H*-imidazo[4,5-*c*]quinoline of Formula XXXIX. The reaction can be carried out as described in step (1) of Reaction Scheme I.

In step (8) of Reaction Scheme IV, a benzyloxy-1*H*-imidazo[4,5-*c*]quinoline of Formula XXXIX is cyclized by an intramolecular displacement of the halogen by the carbamate-protected amino group. The reaction can be carried out as described in step (2) of Reaction Scheme I to provide a compound of Formula XL.

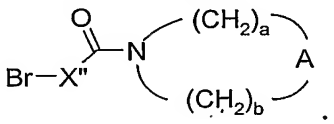
In steps (9) and (10) of Reaction Scheme IV, the Boc protecting group of a 1*H*-imidazo[4,5-*c*]quinoline of Formula XL is first removed to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula XLI or a pharmaceutically acceptable salt thereof. The compound of Formula XLI is then converted to an amide, sulfonamide, urea, or sulfamide of Formula XLII in step (10). Steps (9) and (10) of Reaction Scheme IV can be carried out as described in steps (5a) and (6a) of Route Ia of Reaction Scheme I.

In step (11) of Reaction Scheme IV, the benzyl group of a benzyloxy-1*H*-imidazo[4,5-*c*]quinoline of Formula XLII is cleaved to provide a 1*H*-imidazo[4,5-*c*]quinolinol of Formula XLIII. The cleavage is conveniently carried out on a Parr apparatus under hydrogenolysis conditions using a suitable heterogeneous catalyst such as palladium on carbon in a solvent such as ethanol. Alternatively, the reaction can be carried out by transfer hydrogenation in the presence of a suitable hydrogenation catalyst. The transfer hydrogenation is conveniently carried out by adding ammonium formate to a solution of a benzyloxy-1*H*-imidazo[4,5-*c*]quinoline of Formula XLII in a suitable solvent such as ethanol in the presence of a catalyst such as palladium on carbon. The reaction is

carried out at an elevated temperature, for example, the reflux temperature of the solvent. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (12) of Reaction Scheme IV a 1*H*-imidazo[4,5-*c*]quinolinol of Formula XLIII is converted to an ether-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XLIV using a Williamson-type ether synthesis. The reaction is effected by treating a 1*H*-imidazo[4,5-*c*]quinolinol of Formula XLIII with an alkyl halide of Formula Halide-R_4, Halide-X"-Y'-R_4, or Halide-X"-R_5 in the presence of a base. The reaction is conveniently carried out by combining a reagent of Formula Halide-R_4, Halide-X"-Y'-R_4, or Halide-X"-R_5 with a 1*H*-imidazo[4,5-*c*]quinolinol of Formula XLIII in a solvent such as DMF in the presence of a suitable base such as cesium carbonate. The reaction can be carried out at ambient temperature or at an elevated temperature, for example 65 °C or 85 °C. Alternatively, the reaction can be carried out by treating a solution of a 1*H*-imidazo[4,5-*c*]quinolinol of Formula XLIII in a solvent such as DMF with sodium hydride and then adding a reagent of Formula Halide-R_4, Halide-X"-Y'-R_4, or Halide-X"-R_5. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Numerous reagents of Formulas Halide-R_4 and Halide-X"-Y'-R_4 are commercially available, for example, substituted benzyl bromides and chlorides, substituted or unsubstituted alkyl or arylalkylenyl bromides and chlorides, substituted fluorobenzenes, bromo-substituted ketones, esters, and heterocycles. Other reagents of Formulas Halide-R_4, Halide-X"-Y'-R_4, or Halide-X"-R_5 can be prepared using conventional synthetic methods; for example, a bromo-substituted acid halide of Formula ClC(O)-X"-Br can be treated with a secondary amine in a suitable solvent such as dichloromethane to provide a variety of bromo-substituted amides of Formula Br-X"-C(O)-N(R_8)-R_4 or

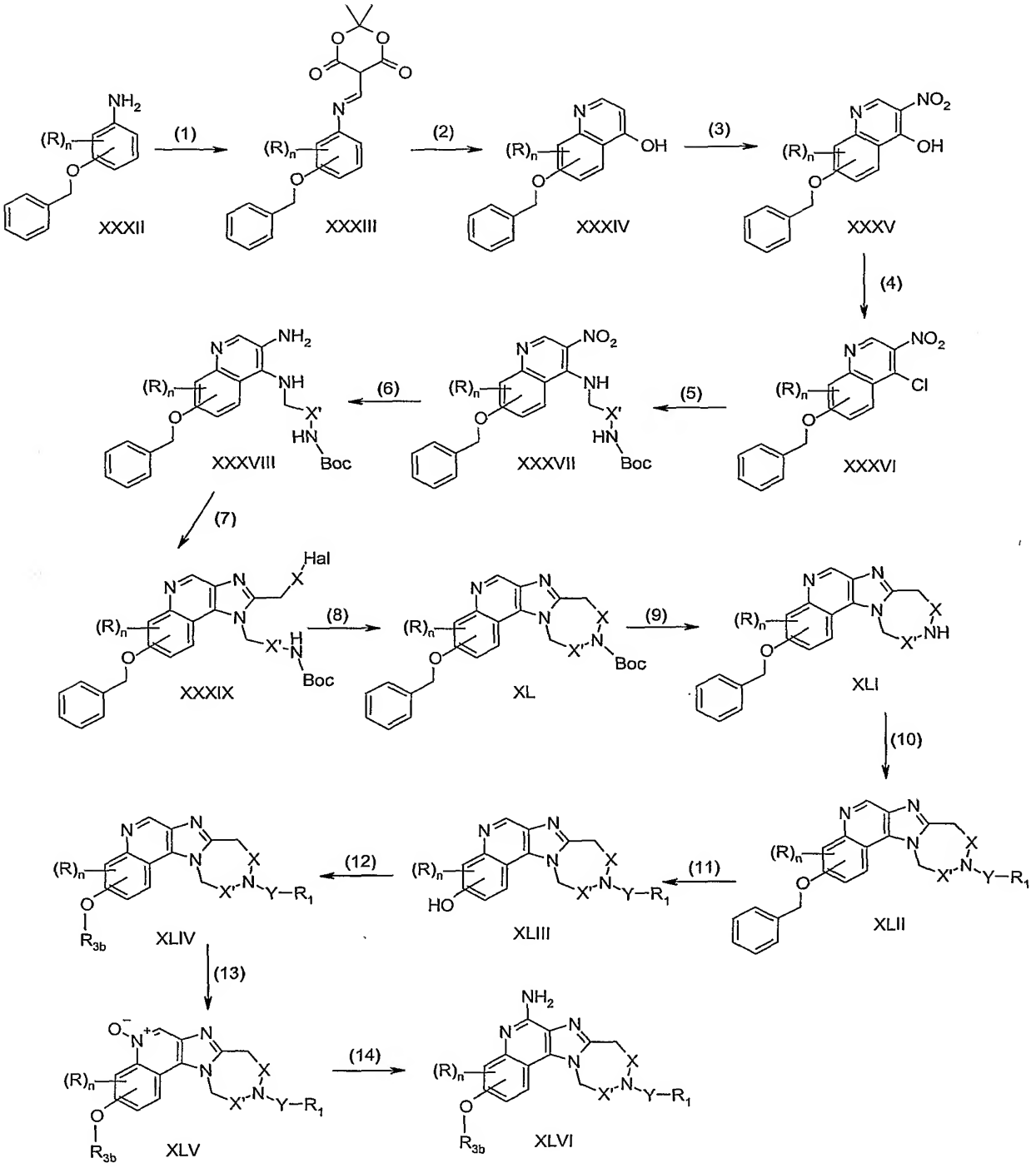


The reaction can be run at a sub-ambient temperature such as -25 °C, and the product can be isolated using conventional methods.

Step (12) of Reaction Scheme IV can alternatively be carried out by treating a 1*H*-imidazo[4,5-*c*]quinolinol of Formula XLIII with an alcohol of Formula HO-X"-Y'-R_4, HO-X"-R_5, or HO-R_4 under Mitsunobu reaction conditions. Numerous alcohols of these formulas are commercially available, and others can be prepared using conventional synthetic methods. The reaction is conveniently carried out by out by adding triphenylphosphine and an alcohol of Formula HO-X"-Y'-R_4, HO-X"-R_5, or HO-R_4 to a solution of a 1*H*-imidazo[4,5-*c*]quinolinol of Formula XLIII in a suitable solvent such as tetrahydrofuran and then slowly adding diisopropyl azodicarboxylate or diethyl azodicarboxylate. The reaction can be carried out at ambient temperature or at a sub-ambient temperature, such as 0 °C. The product can be isolated using conventional methods.

In steps (13) and (14) of Reaction Scheme IV, an ether-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XLIV is first oxidized to a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XLV, which is then aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula XLVI, a subgenus of Formula II. Steps (13) and (14) of Reaction Scheme IV can be carried out as described in steps (3a) and (4a) of Route Ia of Reaction Scheme I. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme IV



Imidazopyridines of the invention can be prepared according to Reaction Scheme V, where R_1, R_{A2}, R_{B2}, X, X', Y, Boc, and Hal are as defined above, and Ph is phenyl. In step (1) of Reaction Scheme V, a 2-phenoxypyridine-3,4-diamine of Formula XLVII is

converted to a 1*H*-imidazo[4,5-*c*]pyridine of Formula XLVIII by reaction with an acid halide of formula Hal-CH_2-X-C(O)Cl or Hal-CH_2-X-C(O)Br or another carboxylic acid equivalent. The reaction can be carried out as described in step (1) of Reaction Scheme I. When X is a bond, the reaction is conveniently carried out by combining a 2-phenoxypyridine-3,4-diamine of Formula XLVII with ethyl chloroacetimidate hydrochloride in a suitable solvent such as chloroform. The reaction can be carried out at an elevated temperature such as 60 °C, and the product can be isolated by conventional methods. Several 2-phenoxypyridine-3,4-diamines of Formula XLVII are known or can be prepared by published methods. See, for example, U. S. Patent No. 6,545,016 and PCT Publication No. WO 03/103584. Ethyl chloroacetimidate hydrochloride is a known compound that can be prepared according to the literature procedure: Stillings, M. R. et al., *J. Med. Chem.*, 29, pp. 2280-2284 (1986).

In step (2) of Reaction Scheme V, a halogen-substituted 1*H*-imidazo[4,5-*c*]pyridine of Formula XLVIII undergoes an intramolecular displacement of the halogen by the carbamate-protected amino group to provide a 4-phenoxy-1*H*-imidazo[4,5-*c*]pyridine of Formula XLIX. The reaction can be carried out as described in step (2) of Reaction Scheme I. Alternatively, the reaction with potassium *tert*-butoxide may be carried out at an elevated temperature such as 60 °C, and a solvent mixture such as THF/dichloromethane can be used. The product can be isolated by conventional methods.

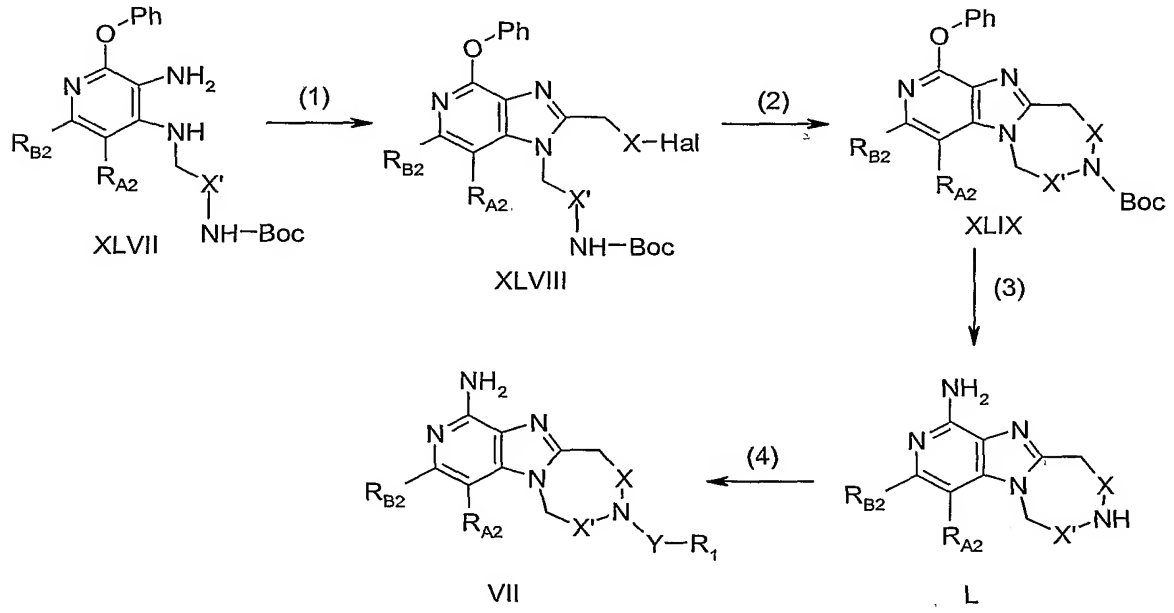
In step (3) of Reaction Scheme V, a 4-phenoxy-1*H*-imidazo[4,5-*c*]pyridine of Formula XLIX is aminated and simultaneously deprotected to provide a 1*H*-imidazo[4,5-*c*]pyridin-4-amine of Formula L, a subgenus of Formulas I, II, and VII. The reaction is conveniently carried out by adding a solution of ammonia in a suitable solvent such as methanol to a compound of Formula XLIX and heating the reaction at an elevated temperature such as 170 °C. Under these conditions, the Boc group of a compound of Formula XLIX is removed to provide a compound of Formula L. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Alternatively, the amination in step (3) may be carried out by heating a 4-phenoxy-1*H*-imidazo[4,5-*c*]pyridine of Formula XLIX with ammonium acetate at an elevated temperature such as 150 °C. This reaction provides a 1*H*-imidazo[4,5-*c*]pyridin-4-amine of Formula VII, wherein Y is -C(O)- and R_1 is methyl. This acetamide can be treated with concentrated hydrochloric acid at an elevated temperature such as 90 °C in a suitable

solvent such as ethanol to provide an amine of Formula L. A 1*H*-imidazo[4,5-*c*]pyridin-4-amine of Formula L or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (4) of Reaction Scheme V, the secondary amine of a 1*H*-imidazo[4,5-*c*]pyridin-4-amine of Formula L or a salt thereof is converted to an amide, sulfonamide, sulfamide, urea, or tertiary amine of Formula VII using one of the methods described in step (6a) of Reaction Scheme I. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Reaction Scheme V



Imidazonaphthyridines of the invention can be prepared according to Reaction Scheme VI, wherein R_1, R, X, X', Y, Boc, Hal, and p are as defined above. In step (1) of Reaction Scheme VI, a naphthyridine-3,4-diamine of Formula LI is reacted with an acid halide of formula Hal-CH_2-X-C(O)Cl or Hal-CH_2-X-C(O)Br or another carboxylic acid equivalent to provide a 1*H*-imidazonaphthyridine of Formula LII. The reaction can be carried out according to either the one-step or two-step procedure described in step (1) of Reaction Scheme I. If the two-step procedure is used, part (ii) of step (1) can be carried out by treating the amide prepared in part (i) with a base such as aqueous sodium hydroxide, aqueous potassium carbonate, or triethylamine to provide a 1*H*-imidazo[4,5-

c][1,5]naphthyridine of Formula LII. The reaction is conveniently carried out in a suitable solvent such as ethanol or in ethanol/water at ambient temperature or at an elevated temperature such as 40 °C. Alternatively, when X is a bond, the reaction can be carried out by combining a naphthyridine-3,4-diamine of Formula LI with ethyl chloroacetimidate hydrochloride under the reaction conditions described in step (1) of Reaction Scheme V. Some compounds of Formula LI are known; others can be prepared using known methods. See, for example, U.S. Patent 6,194,425 (Gerster et al.), particularly Examples 42 and 86.

In step (2) of Reaction Scheme VI, the Boc protecting group of a 1*H*-imidazonaphthyridine of Formula LII is removed under acidic conditions to provide a 1*H*-imidazonaphthyridine of Formula LIII. The deprotection can be carried out using the methods described in step (5a) of Reaction Scheme I, and the product or a salt thereof can be isolated by known methods.

In step (3) of Reaction Scheme VI, the amine of a 1*H*-imidazo[4,5-*c*]naphthyridine of Formula LIII or a salt thereof is converted to an amide, sulfonamide, sulfamide, urea, or secondary amine of Formula LIV using one of the methods described in step (6a) of Reaction Scheme I. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

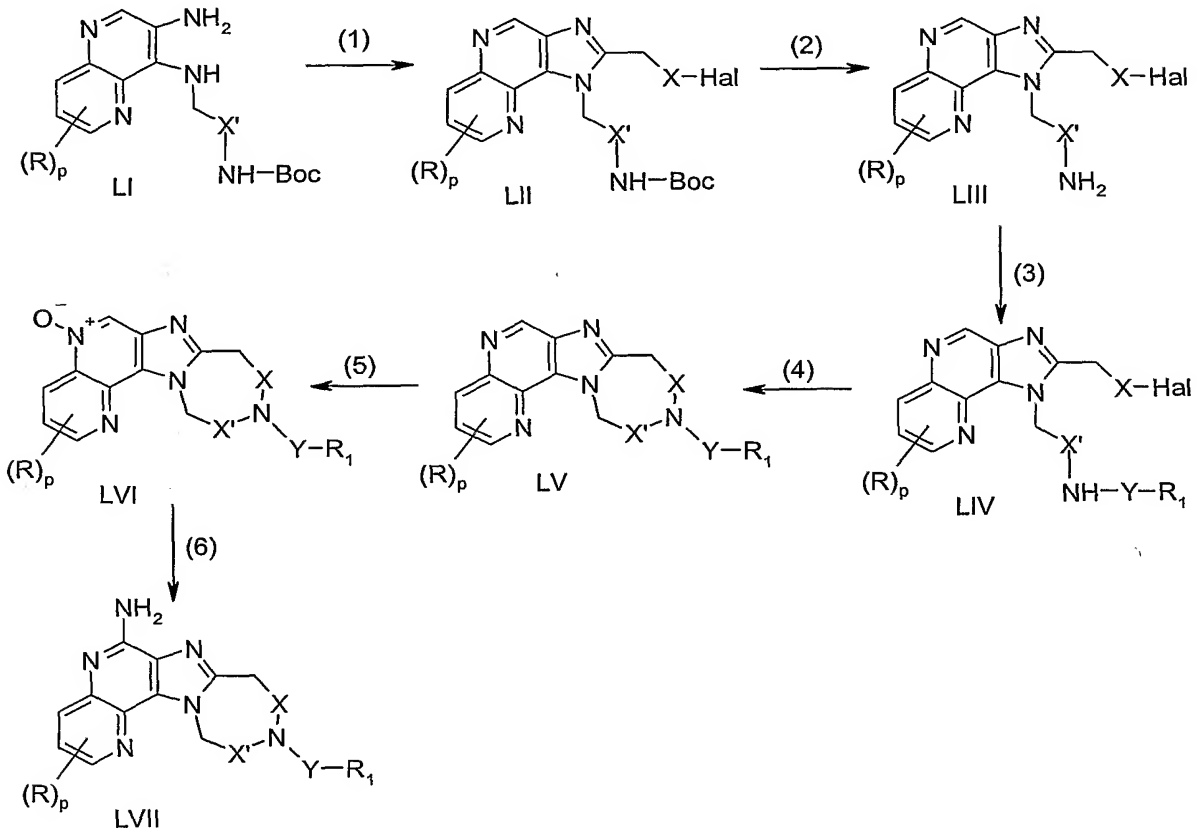
In step (4) of Reaction Scheme VI, a 1*H*-imidazo[4,5-*c*]naphthyridine of Formula LIV undergoes an intramolecular displacement of the halogen by the amide, sulfonamide, sulfamide, urea, or secondary amino group. The reaction can be carried out under the conditions described in step (2) of Reaction Scheme I. Alternatively, a base such as cesium carbonate can be used to effect the cyclization in a solvent such as acetone. The product of Formula V can be isolated by conventional methods.

In steps (5) and (6) of Reaction Scheme VI, a 1*H*-imidazo[4,5-*c*]naphthyridine of Formula LV is first oxidized to a 1*H*-imidazo[4,5-*c*]naphthyridine-5*N*-oxide of Formula LVI, which is then aminated to provide a 1*H*-imidazo[4,5-*c*]naphthyridin-6-amine of Formula LVII, a subgenus of Formulas I, II, and VI. Steps (5) and (6) of Reaction Scheme VI can be carried out according to the methods of steps (3a) and (4a) of Reaction Scheme I. Alternatively, the oxidation and amination can be carried out as a one-pot procedure without isolating the *N*-oxide of Formula LVI by adding 3-chloroperoxybenzoic acid to a solution of a compound of Formula LV in a solvent such as dichloromethane or chloroform and then adding ammonium hydroxide and *p*-toluenesulfonyl chloride. The

product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

A 1*H*-imidazonaphthyridine of Formula LII can also be converted into a 1*H*-imidazo[4,5-*c*]naphthyridin-6-amine of Formula LVII using either Route Ia or Route Ib shown in Reaction Scheme I. In addition a naphthyridine-3,4-diamine of Formula LI can be treated first according to the methods of steps (2) and (3) of Reaction Scheme VI and subsequently treated according to steps (1) through (4) of Reaction Scheme II to provide compounds of Formula LVII.

Reaction Scheme VI



For some embodiments, naphthyridines of the invention can be prepared from tetrazolo compounds of Formulas LVIII and LXII according to Reaction Schemes VII and VIII, wherein R_1, R, X, X', Y, Boc, and p are as defined above. Compounds of Formulas LVIII and LXII can be prepared by known synthetic routes; see, for example, U.S. Patent 6,194,425 (Gerster et al.). The tetrazolo compounds of Formulas LVIII and LXII can each

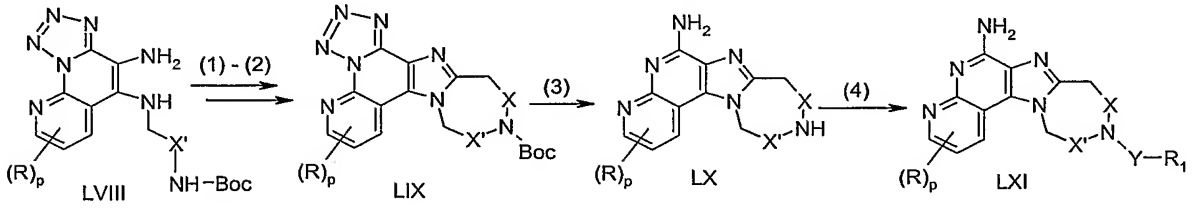
be treated according to the methods of steps (1) and (2) of Reaction Scheme I to provide compounds of Formulas LIX and LXIII, respectively.

In step (3) of Reaction Scheme VII, the tetrazolo and Boc groups are removed from a compound of Formula LIX to provide a 1*H*-imidazo[4,5-*c*]naphthyridin-6-amine of Formula LX. Removal of a tetrazolo group can be carried out in two steps by first treating the compound of Formula LIX with triphenylphosphine and then hydrolyzing the resulting intermediate. The reaction conditions described in U.S. Patent 6,194,425 can be used. Under the hydrolysis conditions, the Boc protecting group is also removed. The product of Formula LX or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

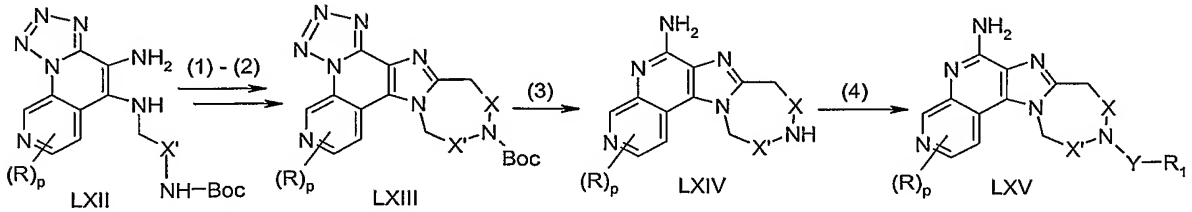
In step (4) of Reaction Scheme VII, the secondary amine of a 1*H*-imidazo[4,5-*c*]naphthyridin-4-amine of Formula LX or a salt thereof is converted to an amide, sulfonamide, sulfamide, urea, or tertiary amine of Formula LXI using one of the methods described in step (6a) of Reaction Scheme I. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Steps (3) and (4) of Reaction Scheme VIII can be carried out in the same manner described for steps (3) and (4) of Reaction Scheme VII, and the products of Formulas LXI and LXV are subgenera Formulas I and II.

Reaction Scheme VII



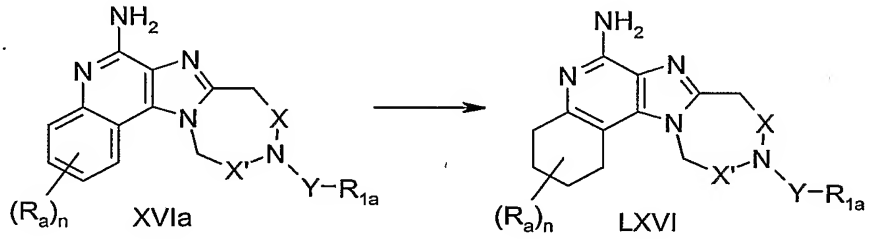
Reaction Scheme VIII



Compounds of the invention can also be prepared according to Reaction Scheme IX, wherein X, X', Y, and n are as defined above; R_a is alkyl, alkoxy, hydroxy, or $-N(R_9)_2$; and R_{1a} is a subset of R_1 as defined above that does not include those substituents that one skilled in the art would recognize as being susceptible to reduction under the acidic hydrogenation conditions of the reaction. These susceptible groups include, for example, alkenyl, alkynyl, and aryl groups and groups bearing nitro substituents.

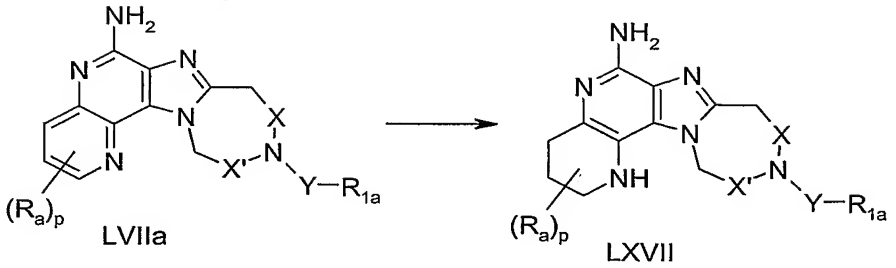
In Reaction Scheme IX, a 1*H*-imidazo[4,5-*c*]quinoline of Formula XVIa is reduced to a tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula LXVI, a subgenus of Formulas I, II, and V. The reaction is conveniently carried out under hetereogeneous hydrogenation conditions by adding platinum (IV) oxide to a solution of the compound of Formula XVIa in trifluoroacetic acid and placing the reaction under hydrogen pressure. The reaction can be carried out on a Parr apparatus at ambient temperature. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Reaction Scheme IX



The reduction described in Reaction Scheme IX can also be used to prepare a tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-6-amine of Formula LXVII, as shown in Reaction Scheme X, wherein X, X', Y, n, R_a, and R_{1a} are as defined above. The product of Formula LXVII, a subgenus of Formulas I and II, or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Reaction Scheme X



Compounds of the invention can also be prepared using variations of the synthetic routes shown in Reaction Schemes I through X that would be apparent to one of skill in the art. For example, the synthetic route shown in Reaction Scheme III for the preparation of quinolines having a R_{3a} substituent can be used to prepare [1,5]naphthyridines having a R_{3a} substituent by using a bromo substituted 4-chloro-3-nitro[1,5]naphthyridine in lieu of the bromo substituted 4-chloro-3-nitroquinoline. Also, a benzyloxy-substitued aminopyridine, in one of several isomeric forms, can be used as the starting material in Reaction Scheme IV to provide a naphthyridine having an R_{3b} substituent. Compounds of the invention can also be prepared using the synthetic routes described in the EXAMPLES below.

Pharmaceutical Compositions and Biological Activity

Pharmaceutical compositions of the invention contain a therapeutically effective amount of a compound or salt of the invention as described above in combination with a pharmaceutically acceptable carrier.

The terms "a therapeutically effective amount" and "effective amount" mean an amount of the compound or salt sufficient to induce a therapeutic or prophylactic effect, such as cytokine induction, immunomodulation, antitumor activity, and/or antiviral activity. Although the exact amount of active compound or salt used in a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art, such as the physical and chemical nature of the compound or salt, the nature of the carrier, and the intended dosing regimen, it is anticipated that the compositions of the invention will contain sufficient active ingredient to provide a dose of about 100 nanograms per kilogram (ng/kg) to about 50 milligrams per kilogram (mg/kg), preferably about 10 micrograms per kilogram (μg/kg) to about 5 mg/kg, of the compound or salt to

the subject. A variety of dosage forms may be used, such as tablets, lozenges, capsules, parenteral formulations, syrups, creams, ointments, aerosol formulations, transdermal patches, transmucosal patches and the like.

The compounds or salts of the invention can be administered as the single therapeutic agent in the treatment regimen, or the compounds or salts of the invention may be administered in combination with one another or with other active agents, including additional immune response modifiers, antivirals, antibiotics, antibodies, proteins, peptides, oligonucleotides, etc.

Compounds or salts of the invention have been shown to induce and/or inhibit the production of certain cytokines in experiments performed according to the tests set forth below. These results indicate that the compounds or salts are useful as immune response modifiers that can modulate the immune response in a number of different ways, rendering them useful in the treatment of a variety of disorders.

Cytokines whose production may be induced by the administration of compounds or salts of the invention generally include interferon-α (IFN-α) and/or tumor necrosis factor-α (TNF-α) as well as certain interleukins (IL). Cytokines whose biosynthesis may be induced by compounds or salts of the invention include IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12, and a variety of other cytokines. Among other effects, these and other cytokines can inhibit virus production and tumor cell growth, making the compounds or salts useful in the treatment of viral diseases and neoplastic diseases. Accordingly, the invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt or composition of the invention to the animal. The animal to which the compound or salt or composition is administered for induction of cytokine biosynthesis may have a disease as described *infra*, for example a viral disease or a neoplastic disease, and administration of the compound or salt may provide therapeutic treatment. Alternatively, the compound or salt may be administered to the animal prior to the animal acquiring the disease so that administration of the compound or salt may provide a prophylactic treatment.

In addition to the ability to induce the production of cytokines, compounds or salts of the invention can affect other aspects of the innate immune response. For example, natural killer cell activity may be stimulated, an effect that may be due to cytokine induction. The compounds or salts may also activate macrophages, which in turn

stimulate secretion of nitric oxide and the production of additional cytokines. Further, the compounds or salts may cause proliferation and differentiation of B-lymphocytes.

Compounds or salts of the invention can also have an effect on the acquired immune response. For example, the production of the T helper type 1 (T_H1) cytokine IFN-γ may be induced indirectly and the production of the T helper type 2 (T_H2) cytokines IL-4, IL-5, and IL-13 may be inhibited upon administration of the compounds or salts.

Other cytokines whose production may be inhibited by the administration of compounds or salts of the invention include tumor necrosis factor-α (TNF-α). Among other effects, inhibition of TNF-α production can provide prophylaxis or therapeutic treatment of TNF-α mediated diseases in animals, making the compounds or salt useful in the treatment of, for example, autoimmune diseases. Accordingly, the invention provides a method of inhibiting TNF-α biosynthesis in an animal comprising administering an effective amount of a compound or salt or composition of the invention to the animal. The animal to which the compound or salt or composition is administered for inhibition of TNF-α biosynthesis may have a disease as described *infra*, for example an autoimmune disease, and administration of the compound or salt may provide therapeutic treatment. Alternatively, the compound or salt may be administered to the animal prior to the animal acquiring the disease so that administration of the compound or salt may provide a prophylactic treatment.

Whether for prophylaxis or therapeutic treatment of a disease, and whether for effecting innate or acquired immunity, the compound or salt or composition may be administered alone or in combination with one or more active components as in, for example, a vaccine adjuvant. When administered with other components, the compound or salt and other component or components may be administered separately; together but independently such as in a solution; or together and associated with one another such as (a) covalently linked or (b) non-covalently associated, e.g., in a colloidal suspension.

Conditions for which IRMs identified herein may be used as treatments include, but are not limited to:

(a) viral diseases such as, for example, diseases resulting from infection by an adenovirus, a herpesvirus (e.g., HSV-I, HSV-II, CMV, or VZV), a poxvirus (e.g., an orthopoxvirus such as variola or vaccinia, or molluscum contagiosum), a picornavirus (e.g., rhinovirus or enterovirus), an orthomyxovirus (e.g., influenzavirus), a paramyxovirus

(e.g., parainfluenzavirus, mumps virus, measles virus, and respiratory syncytial virus (RSV)), a coronavirus (e.g., SARS), a papovavirus (e.g., papillomaviruses, such as those that cause genital warts, common warts, or plantar warts), a hepadnavirus (e.g., hepatitis B virus), a flavivirus (e.g., hepatitis C virus or Dengue virus), or a retrovirus (e.g., a lentivirus such as HIV);

(b) bacterial diseases such as, for example, diseases resulting from infection by bacteria of, for example, the genus Escherichia, Enterobacter, Salmonella, Staphylococcus, Shigella, Listeria, Aerobacter, Helicobacter, Klebsiella, Proteus, Pseudomonas, Streptococcus, Chlamydia, Mycoplasma, Pneumococcus, Neisseria, Clostridium, Bacillus, Corynebacterium, Mycobacterium, Campylobacter, Vibrio, Serratia, Providencia, Chromobacterium, Brucella, Yersinia, Haemophilus, or Bordetella;

(c) other infectious diseases, such chlamydia, fungal diseases including but not limited to candidiasis, aspergillosis, histoplasmosis, cryptococcal meningitis, or parasitic diseases including but not limited to malaria, pneumocystis carnii pneumonia, leishmaniasis, cryptosporidiosis, toxoplasmosis, and trypanosome infection;

(d) neoplastic diseases, such as intraepithelial neoplasias, cervical dysplasia, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, renal cell carcinoma, Kaposi's sarcoma, melanoma, leukemias including but not limited to myelogeous leukemia, chronic lymphocytic leukemia, multiple myeloma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, B-cell lymphoma, and hairy cell leukemia, and other cancers;

(e) T_H2-mediated, atopic diseases, such as atopic dermatitis or eczema, eosinophilia, asthma, allergy, allergic rhinitis, and Ommen's syndrome;

(f) certain autoimmune diseases such as systemic lupus erythematosus, essential thrombocythaemia, multiple sclerosis, discoid lupus, alopecia areata; and

(g) diseases associated with wound repair such as, for example, inhibition of keloid formation and other types of scarring (e.g., enhancing wound healing, including chronic wounds).

Additionally, an IRM compound or salt of the present invention may be useful as a vaccine adjuvant for use in conjunction with any material that raises either humoral and/or cell mediated immune response, such as, for example, live viral, bacterial, or parasitic immunogens; inactivated viral, tumor-derived, protozoal, organism-derived, fungal, or bacterial immunogens, toxoids, toxins; self-antigens; polysaccharides; proteins;

glycoproteins; peptides; cellular vaccines; DNA vaccines; autologous vaccines; recombinant proteins; and the like, for use in connection with, for example, BCG, cholera, plague, typhoid, hepatitis A, hepatitis B, hepatitis C, influenza A, influenza B, parainfluenza, polio, rabies, measles, mumps, rubella, yellow fever, tetanus, diphtheria, hemophilus influenza b, tuberculosis, meningococcal and pneumococcal vaccines, adenovirus, HIV, chicken pox, cytomegalovirus, dengue, feline leukemia, fowl plague, HSV-1 and HSV-2, hog cholera, Japanese encephalitis, respiratory syncytial virus, rotavirus, papilloma virus, yellow fever, and Alzheimer's Disease.

Certain IRM compounds or salts of the present invention may be particularly helpful in individuals having compromised immune function. For example, certain compounds or salts may be used for treating the opportunistic infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

Thus, one or more of the above diseases or types of diseases, for example, a viral disease or a neoplastic disease may be treated in an animal in need thereof (having the disease) by administering a therapeutically effective amount of a compound or salt of the invention to the animal.

An amount of a compound or salt effective to induce or inhibit cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as monocytes, macrophages, dendritic cells and B-cells to produce an amount of one or more cytokines such as, for example, IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12 that is increased (induced) or decreased (inhibited) over a background level of such cytokines. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. The invention also provides a method of treating a viral infection in an animal and a method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or salt or composition of the invention to the animal. An amount effective to treat or inhibit a viral infection is an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount that is effective for such treatment will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to

about 5 mg/kg. An amount of a compound or salt effective to treat a neoplastic condition is an amount that will cause a reduction in tumor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg.

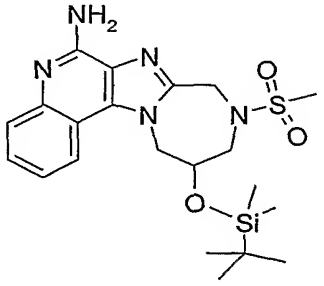
Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

EXAMPLES

In the examples below, some of the compounds were purified by preparative high performance liquid chromatography (prep HPLC) using a Waters Fraction Lynx automated purification system. The prep HPLC fractions were analyzed using a Micromass LC/TOF-MS, and the appropriate fractions were combined and centrifuge evaporated to provide the trifluoroacetate salt of the desired compound. In order to maximize purity, some of the compounds were sent through the purification process twice. A variety of chromatographic conditions were used for separations. Column: Phenomenex LUNA C18(2), 21.2 x 50 millimeters (mm), 10 micron particle size; or Waters XTERRA C18, 19 x 50 millimeters (mm), 5 micron particle size; non-linear gradient elution from 5 to 95% B where A is 0.05% trifluoroacetic acid/water and B is 0.05% trifluoroacetic acid/acetonitrile; fraction collection by mass-selective triggering.

Example 1

11-{[*tert*-Butyl(dimethyl)silyl]oxy}-9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine



Part A

Under a nitrogen atmosphere, a solution of di-*tert*-butyl dicarbonate (145.35 g, 665.98 mmol) in 1,4-dioxane (400 mL) was added dropwise with stirring to a solution of 2-hydroxy-1,3-diaminopropane (300.00 g, 332.85 mmol) in methanol (500 mL) over a period of six hours. The reaction was stirred overnight at ambient temperature and then concentrated under reduced pressure. The residue was dissolved in 10% citric acid in water, and additional citric acid was added to adjust the solution to pH 4. The resulting solution (1-1.5 L) was washed with dichloromethane (3 x 500 mL) and then adjusted to pH 12 with the addition of 50% aqueous sodium hydroxide. The basic solution was extracted with chloroform (7 x 500 mL), and the combined extracts were concentrated under reduced pressure and dried overnight under high vacuum to provide 108.19 g of *tert*-butyl 3-amino-2-hydroxypropylcarbamate as a white solid.

Part B

Under a nitrogen atmosphere, triethylamine (72 g, 710 mmol) was added to a solution of 4-chloro-3-nitroquinoline (98.9 g, 474 mmol) in *N,N*-dimethylformamide (DMF) (1 L). A solution of *tert*-butyl 3-amino-2-hydroxypropylcarbamate (108.19 g, 569 mmol) in dioxane (800 mL) was slowly added, and the reaction was stirred overnight at ambient temperature and then poured into water (3 L) with continuous stirring. A precipitate formed and was isolated by filtration, washed with water, and dried for three days in a vacuum oven at 65 °C to provide 167.54 g of *tert*-butyl 2-hydroxy-3-[(3-nitroquinolin-4-yl)amino]propylcarbamate as a bright yellow powder.

Part C

Triethylamine (111.7 g, 1.104 mol) was added to a solution of *tert*-butyl 2-hydroxy-3-[(3-nitroquinolin-4-yl)amino]propylcarbamate (100.0 g, 275.95 mmol) in DMF (400 mL). A solution of *tert*-butyldimethylsilyl chloride (TBDMSCl) (91.5 g, 607 mmol) in DMF (140 mL) was slowly added, and the reaction was stirred overnight at ambient temperature. An analysis by high-performance liquid chromatography (HPLC) indicated the presence of starting material, and additional triethylamine (1 equivalent) and TBDMSCl (0.5 equivalent) were added. The reaction was stirred overnight at ambient temperature, and a large excess of TBDMSCl was added. The product mixture was filtered to remove a solid, and the filtrate was concentrated under reduced pressure. The residue was dissolved in chloroform, and the resulting solution was washed with aqueous ammonium chloride (3 x), aqueous sodium bicarbonate (2 x), and brine and then concentrated under reduced pressure. The resulting solid was dried overnight under high vacuum. The crude solid was recrystallized from acetonitrile, and two crops of crystals were collected to provide 110.18 g of *tert*-butyl 2-{[*tert*-butyl(dimethyl)silyl]oxy}-3-[(3-nitroquinolin-4-yl)amino]propylcarbamate as a white powder.

Part D

A solution of *tert*-butyl 2-{[*tert*-butyl(dimethyl)silyl]oxy}-3-[(3-nitroquinolin-4-yl)amino]propylcarbamate (110.18 g, 231.16 mmol) in dichloromethane (500 mL) was added to a Parr vessel. The system was purged with nitrogen, and 10% palladium on carbon (14.76 g, 138.7 mmol) was added. The vessel was placed under hydrogen pressure (30 psi, 2.1 x 10^5 Pa) and shaken for four hours. The reaction mixture was filtered, and the filtrate was passed through a plug of silica gel and concentrated under reduced pressure to provide 103.45 g of *tert*-butyl 3-[(3-aminoquinolin-4-yl)amino]-2-{[*tert*-butyl(dimethyl)silyl]oxy}propylcarbamate.

Part E

Triethylamine (46.2 g, 456 mmol) was added to a solution of *tert*-butyl 3-[(3-aminoquinolin-4-yl)amino]-2-{[*tert*-butyl(dimethyl)silyl]oxy}propylcarbamate (101.9 g, 228.1 mmol) in 1,2-dichloroethane (600 mL). A solution of chloroacetyl chloride (28.3 g, 251 mmol) in 1,2-dichloroethane was added dropwise, and the reaction was stirred

overnight at ambient temperature. The reaction mixture was filtered to remove a solid, and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluting sequentially with 95.5:0.5 and 95:5 dichloromethane:methanol), and the purified product was dried overnight under high vacuum to provide 71.93 g of *tert*-butyl 2-{[*tert*-butyl(dimethyl)silyl]oxy}-3-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propylcarbamate.

Part F

Potassium *tert*-butoxide (116.1 mL of a 1M solution in tetrahydrofuran) was added to a solution of *tert*-butyl 2-{[*tert*-butyl(dimethyl)silyl]oxy}-3-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propylcarbamate (42.72 g, 84.57 mmol) in anhydrous tetrahydrofuran (THF) (50 mL), and the reaction was stirred overnight at ambient temperature and then concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluting with dichloromethane:methanol in a gradient from 99:1 to 95:5) to provide 20.23 g of *tert*-butyl 11-{[*tert*-butyl(dimethyl)silyl]oxy}-11,12-dihydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(10*H*)-carboxylate.

Part G

Trifluoroacetic acid (500 mL of a 10% solution in dichloromethane) was added to *tert*-butyl 11-{[*tert*-butyl(dimethyl)silyl]oxy}-11,12-dihydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(10*H*)-carboxylate (9.23 g, 19.7 mmol), and the reaction was stirred at ambient temperature for 75 minutes. The solvent was removed under reduced pressure, and the residue was shaken with triethylamine (300 mL) and dichloromethane. The solution was concentrated under reduced pressure, and the product was dried under high vacuum for two hours to provide 11-{[*tert*-butyl(dimethyl)silyl]oxy}-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline, which was used in the next step without removing the triethylamine trifluoroacetate salt.

Part H

Triethylamine (7.97 g, 78.8 mmol) was added to a solution of the material from Part G in dichloromethane (500 mL). Methanesulfonyl chloride (2.71 g, 23.6 mmol) was slowly added. The reaction was stirred at ambient temperature for one hour, washed with brine and sodium bicarbonate, and concentrated under reduced pressure. The residue was dried for two days under high vacuum to provide 8.78 g of 11-{[*tert*-butyl(dimethyl)silyl]oxy}-9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline. The product was combined with material made in a separate run.

Part I

3-Chloroperoxybenzoic acid (9.92 g of 77% pure material, 57.47 mmol) (mCPBA) was added to a solution of 11-{[*tert*-butyl(dimethyl)silyl]oxy}-9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline (16.47 g, 36.88 mmol) in chloroform (200 mL), and the reaction was stirred overnight at ambient temperature. Additional mCPBA (1-1.5 equivalents) was added, and the reaction was stirred for two hours, washed with brine and sodium bicarbonate, and concentrated under reduced pressure.

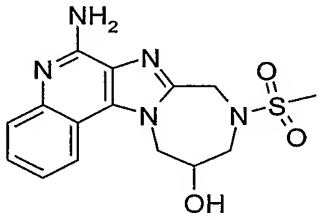
Part J

Ammonium hydroxide (150 mL) was added with vigorous stirring to a solution of the material from Part I in chloroform (200 mL). *p*-Toluenesulfonyl chloride (7.73 g, 40.6 mmol) was added in portions, and the reaction was stirred overnight and then concentrated under reduced pressure. The residue was dissolved in chloroform and poured into ethyl acetate (800 mL) to form a precipitate, which was isolated by filtration and washed with methanol. The filtrate was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate (50 mL) and refrigerated overnight. Crystals formed and were isolated by filtration, and two additional crops of crystals were obtained in the same manner. The crystals were combined and dried in a vacuum oven to provide 6.69 g of 11-{[*tert*-butyl(dimethyl)silyl]oxy}-9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine as white crystals, mp 256-258 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.12 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.3 Hz, 1H), 7.33

(t, J = 7.3 Hz, 1H), 7.12 (t, J = 8.1 Hz, 1H), 6.52 (s, 2H), 5.08 (dd, J = 15.2, 6.22 Hz, 1H), 4.83 – 4.69 (m, 3H), 4.26 (br s, 1H), 3.78 (dd, J = 14.6, 3.9 Hz, 1H), 3.61 (dd, J = 14.4, 1.61 Hz, 1H), 2.67 (s, 3H), 0.51 (s, 9H), 0.00 (s, 3H), -0.19 (s, 3H);
MS (APCI) *m/z* 462.1 $(M + H)^+$;
Anal. Calcd for $C_{21}H_{31}N_5O_3SSi$: C, 54.63; H, 6.77; N, 15.17 Found: C, 54.50; H, 6.48; N, 14.99.

Example 2

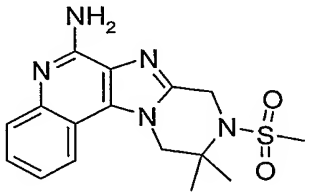
6-Amino-9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-11-ol



A suspension of 11-{[*tert*-butyl(dimethyl)silyl]oxy}-9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine (1.0 g, 2.2 mmol) in anhydrous THF (30 mL) was cooled to -20 °C, and tetrabutylammonium fluoride (2.383 mL of a 1 M solution in THF) was slowly added. The reaction was stirred overnight, and a precipitate formed. The cold reaction mixture was filtered, and the isolated precipitate was washed with THF and dried under high vacuum to provide 313.7 mg of 6-amino-9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-11-ol as white crystals, mp 282-283 °C.
^{1}H NMR (300 MHz), DMSO, δ 8.30 (d, J = 8.1 Hz, 1H), 7.61 (d, J = 8.2 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.22 (t, J = 8.0 Hz, 1H), 6.59 (s, 2H), 5.74 (s, 1H), 5.09 (dd, J = 14.8, 6.7 Hz, 1H), 4.86-4.78 (m, 3H), 4.15 (s, 1H), 3.84-3.69 (m, 2H), 2.71 (s, 3H);
MS (APCI) *m/z* 348.1 $(M + H)^+$;
Anal. Calcd for $C_{15}H_{17}N_5O_3S \bullet 0.4H_2O$: C, 50.81; H, 5.06; N, 19.75 Found: C, 51.02; H, 5.21; N, 19.58.

Example 3

10,10-Dimethyl-9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine



Part A

Under a nitrogen atmosphere, a solution of triethylamine (167 mL, 1.20 mol) in anhydrous dichloromethane (1 L) was cooled to 0 °C. Solid 4-chloro-3-nitroquinoline (121.6 g, 585 mmol) was added over a period of five minutes, and the reaction was allowed to warm to ambient temperature slowly and stirred for two days. The solvent was removed under reduced pressure, and the resulting yellow solid was shaken with water (1 L) for several minutes and then isolated by filtration, washed with water (3 x 200 mL), and dried under vacuum for four days to provide 149 g of 2-methyl-N^1-(3-nitroquinolin-4-yl)propane-1,2-diamine as a bright yellow powder.

Anal. Calcd for $C_{13}H_{16}N_4O_2$: C, 59.53; H, 6.23; N, 21.36. Found: C, 59.23; H, 6.22; N, 21.45.

The product was dissolved in isopropanol (2 x 100 mL), concentrated under reduced pressure, dissolved in chloroform (2 x 100 mL), concentrated under reduced pressure, and finally dried under vacuum overnight.

Part B

Under a nitrogen atmosphere, a suspension of 2-methyl-N^1-(3-nitroquinolin-4-yl)propane-1,2-diamine (93 g, 358 mmol) and triethylamine (100 mL, 717 mmol) in anhydrous dichloromethane (1 L) was cooled to 0 °C. Methanesulfonyl chloride (27.7 mL, 358 mmol) was added over a period of 20 minutes. The reaction was allowed to warm to ambient temperature and stirred overnight. Additional methanesulfonyl chloride (9.2 mL) was added over a period of five minutes, and the reaction was stirred for an additional day. Additional methanesulfonyl chloride (2.0 mL) was added, and the reaction was stirred for two hours. The solvent was removed under reduced pressure, and the residue was triturated with water (800 mL) at 50 °C, isolated by filtration, and washed

with water to provide 116 g of *N*-{1,1-dimethyl-2-[(3-nitroquinolin-4-yl)amino]ethyl}methanesulfonamide as a yellow powder.

Part C

A solution of *N*-{1,1-dimethyl-2-[(3-nitroquinolin-4-yl)amino]ethyl}methanesulfonamide (4.0 g, 12 mmol) in acetonitrile (200 mL) was added to a Parr vessel charged with 5% platinum on carbon (0.5 g) and purged with nitrogen. The vessel was placed under hydrogen pressure (50 psi, 3.4 x 10^5 Pa) and shaken overnight. The reaction was filtered through a layer of CELITE filter aid, and the filter cake was washed with acetonitrile and dichloromethane until the filtrate was colorless. The filtrate was concentrated under reduced pressure to provide 3.51 g of *N*-{2-[(3-aminoquinolin-4-yl)amino]-1,1-dimethylethyl}methanesulfonamide as a yellow powder.

Part D

Under a nitrogen atmosphere, a solution of *N*-{2-[(3-aminoquinolin-4-yl)amino]-1,1-dimethylethyl}methanesulfonamide (2.65 g, 8.59 mmol) in 1,2-dichloroethane (100 mL) was cooled to 0 °C. Triethylamine (2.4 mL, 17 mmol) and chloroacetyl chloride (0.82 mL, 10.3 mmol) were sequentially added, and the reaction was allowed to warm to ambient temperature, stirred overnight, and then heated at reflux for 1.5 days. The reaction was washed with saturated aqueous sodium bicarbonate (2 x 100 mL) and brine (100 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide 1.92 g of 10,10-dimethyl-9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[4',3':1,2]imidazo[4,5-*c*]quinoline as a brown solid, which was used without purification.

Part E

In one portion mCPBA (0.87 g of 60% purity, 3.0 mmol) was added to a solution of 10,10-dimethyl-9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[4',3':1,2]imidazo[4,5-*c*]quinoline (0.98 g, 3.0 mmol) in chloroform (50 mL), and the reaction was stirred for three hours at ambient temperature under a nitrogen atmosphere. The reaction mixture was washed with 1% aqueous sodium carbonate (50 mL), and the aqueous solution was extracted with chloroform (3 x 50 mL). The combined organic fractions were washed

with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide 0.91 g of 10,10-dimethyl-9-(methylsulfonyl)-5-oxido-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinoline as an orange solid.

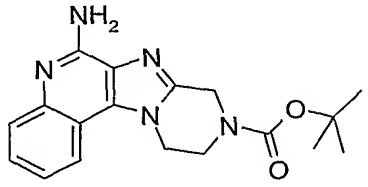
Part F

Ammonium hydroxide (5 mL) was added with vigorous stirring to a suspension of 10,10-dimethyl-9-(methylsulfonyl)-5-oxido-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinoline (0.91 g, 2.6 mmol) in dichloromethane (25 mL). *p*-Toluenesulfonyl chloride (0.50 g, 2.6 mmol) was added in one portion, and the reaction was stirred for four hours at ambient temperature. The organic layer was separated and washed with 1% aqueous sodium carbonate (50 mL) and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting orange solid (0.77 g) was recrystallized from 1,2-dichloroethane to provide 10,10-dimethyl-9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine as a white powder, mp 227-228 °C.

Anal. Calcd for $C_{16}H_{19}N_5O_2S$: C, 55.64; H, 5.54; N, 20.27. Found: C, 55.35; H, 5.61; N, 20.07.

Example 4

tert-Butyl 6-amino-10,11-dihydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(8*H*)-carboxylate



Part A

Triethylamine (58.2 g, 575 mmol) and 4-chloro-3-nitroquinoline (80.0 g, 384 mmol) were added to a solution of *tert*-butyl *N*-(2-aminoethyl)carbamate (67.6 g, 422 mmol) in DMF (300 mL), and the reaction was stirred overnight at ambient temperature. Water (600 mL) was added, and the resulting mixture was stirred for one hour. A precipitate formed and was isolated by filtration, washed with water (3 x 150 mL), and

dried for two days in a vacuum oven at 45 °C to provide 125.36 g of *tert*-butyl 2-[(3-nitroquinolin-4-yl)amino]ethylcarbamate as a yellow solid.

Part B

A solution of *tert*-butyl 2-[(3-nitroquinolin-4-yl)amino]ethylcarbamate (20.0 g, 60.2 mmol) in a 2:1 mixture of dichloromethane:methanol (500 mL) was added to a Parr vessel. The system was purged with nitrogen, and 5% platinum on carbon (7.04 g, 36.1 mmol) was added. The vessel was placed under hydrogen pressure (50 psi, 3.4 x 10^5 Pa) and shaken overnight. The reaction mixture was filtered and concentrated under reduced pressure to provide 15.65 g of *tert*-butyl 2-[(3-aminoquinolin-4-yl)amino]ethylcarbamate.

Part C

A modification of the method described in Part E of Example 1 was used to treat *tert*-butyl 2-[(3-aminoquinolin-4-yl)amino]ethylcarbamate (15.65 g, 51.76 mmol) with triethylamine (10.82 mL, 77.64 mmol) followed by chloroacetyl chloride (4.5 mL, 57 mmol). The reaction was carried out in dichloromethane (60 mL). After the reaction mixture was filtered, the filtrate was washed with dilute aqueous sodium bicarbonate, dried over magnesium sulfate, and concentrated under reduced pressure to provide *tert*-butyl 2-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethylcarbamate as an amber-colored solid, which was combined with material from two other runs for use in the next step.

Part D

Under a nitrogen atmosphere, a solution of *tert*-butyl 2-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethylcarbamate (54.94 g, 152.3 mmol) in THF (400 mL) was cooled to 0 °C; a solution of potassium *tert*-butoxide (18.79 g of a 1 M solution in THF, 167.5 mmol) was added slowly. The reaction was stirred at 0 °C for three hours and then at ambient temperature overnight. The THF was removed under reduced pressure, and a 1:1 mixture of water and saturated aqueous sodium bicarbonate was added. The aqueous mixture was extracted with dichloromethane, and the combined extracts were washed sequentially with water and brine and concentrated under reduced pressure to provide

29.54 g of *tert*-butyl 10,11-dihydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(8*H*)-carboxylate.

Part E

mCPBA (26.1 g of 77% pure material, 118 mmol) was added in small portions to a solution of *tert*-butyl 10,11-dihydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(8*H*)-carboxylate (29.54 g, 91.06 mmol) in chloroform (500 mL), and the reaction was stirred for one hour at ambient temperature. Aqueous sodium carbonate (400 mL of a 1% solution) was added, and the mixture was stirred for 30 minutes. The organic layer was separated, washed with 1% aqueous sodium carbonate (2 x 300 mL). Citric acid (10% aqueous solution) was added to aid in the separation. The organic layer was then washed twice with 10% aqueous citric acid, and the combined aqueous washings were extracted with chloroform (3 x 150 mL). The combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting solid was dried overnight under vacuum to provide 28.49 g of *tert*-butyl 5-oxido-10,11-dihydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(8*H*)-carboxylate as a brown solid.

Part F

Concentrated ammonium hydroxide (160 mL) was added with vigorous stirring to a solution of *tert*-butyl 5-oxido-10,11-dihydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(8*H*)-carboxylate (28.49 g, 83.7 mmol) in dichloromethane (300 mL). *p*-Toluenesulfonyl chloride (15.96 g, 83.7 mmol) was added in small portions over a period of five minutes, after which an analysis by HPLC indicated that the reaction was complete. The aqueous layer was then extracted with dichloromethane (3 x 150 mL), and the combined organic fractions were washed with 1% aqueous sodium carbonate (2 x 150 mL). The combined aqueous washings were extracted with dichloromethane (200 mL), and all organic fractions were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide *tert*-butyl 6-amino-10,11-dihydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(8*H*)-carboxylate as a yellow solid.

Material from another run was purified by column chromatography on silica gel (eluting with dichloromethane:methanol in a gradient from 99:1 to 85:15) to provide the product as a white powder, mp 207°C

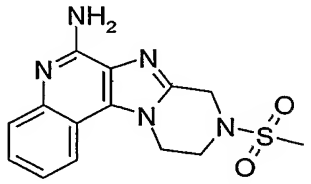
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 8.2 Hz, 1H), 7.49 (t, J = 7.2 Hz, 1H), 7.27 (t, J = 7.6 Hz, 1H), 5.51 (s, 2H), 4.92 (s, 2H), 4.53 (t, J = 5.4 Hz, 2H), 4.03 (t, J = 5.4 Hz, 2H), 1.53 (s, 9H);

MS (APCI) *m/z* 340 $(M + H)^+$;

Anal. Calcd for $C_{18}H_{21}N_5O_2$: C, 63.70; H, 6.24; N, 20.63. Found: C, 63.65; H, 6.51; N, 20.52.

Example 5

9-(Methylsulfonyl)-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine trifluoroacetate



Part A

Hydrogen chloride (300 mL of a 4 N solution in 1,4-dioxane) was added to a solution of *tert*-butyl 6-amino-10,11-dihydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(8*H*)-carboxylate (34.74 g, 102.36 mmol) in dichloromethane (300 mL). The reaction was stirred overnight at ambient temperature and then concentrated under reduced pressure. The resulting solid was suspended in dichloromethane, isolated by filtration, and washed sequentially with dichloromethane, diethyl ether, hexane, and diethyl ether. The solid was then triturated with methanol and isolated by filtration to provide 11.58 g of 8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine hydrochloride as a white solid. The filtrate was concentrated under reduced pressure, dissolved in water, and precipitated with 1,4-dioxane to provide an additional 6.95 g of product.

Part B

Triethylamine (2.8 mL, 20.1 mmol) was added to a suspension of 8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine hydrochloride (1.85 g, 6.71 mmol) in DMF (20 mL). The mixture was sonicated for ten minutes at 80 °C, and methanesulfonyl chloride (922 mg, 8.05 mmol) was slowly added. The mixture was stirred at ambient temperature overnight. After the solvent was removed under reduced

pressure, the residue was combined with material from two other runs and ultimately purified by prep HPLC according to the method described above to provide 9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine trifluoroacetate as white crystals, mp 242-243 °C.

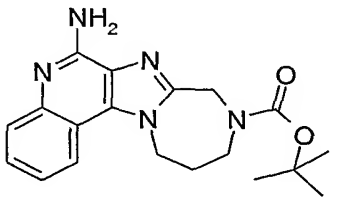
^{1}H NMR (300 MHz, DMSO-d_6) δ 9.06 (br s, 2H), 8.26 (d, J = 8.13 Hz, 1H), 7.82 (d, J = 8.31 Hz, 1H), 7.73 (t, J = 7.21 Hz, 1H), 7.57 (t, J = 7.21 Hz, 1H), 4.83 (t, J = 5.37 Hz, 2H), 4.78 (s, 2H), 3.88 (t, J = 5.36 Hz, 2H), 3.18 (s, 3H);

^{13}C NMR (75 MHz, DMSO-d_6) δ 149.6, 147.5, 135.2, 134.5, 130.0, 125.1, 124.8, 122.4, 119.0, 113.2, 46.1, 45.0, 42.5, 36.5;

HRMS: Calc for $C_{14}H_{15}N_5O_2$, theoretical mass 318.1025, measured mass 318.1015.

Example 6

tert-Butyl 6-amino-11,12-dihydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(10*H*)-carboxylate



Part A

4-Chloro-3-nitroquinoline (54.42 g, 260.9 mmol) was added to a solution of *tert*-butyl *N*-(3-aminopropyl)carbamate (50.0 g, 287 mmol) in anhydrous DMF (300 mL), and the reaction was stirred overnight at ambient temperature. The product was isolated as described in Part A of Example 4 to provide 84.55 g of *tert*-butyl 3-[(3-nitroquinolin-4-yl)amino]propylcarbamate as a yellow solid.

Part B

A solution of *tert*-butyl 3-[(3-nitroquinolin-4-yl)amino]propylcarbamate (50.0 g, 144 mmol) in 1,2-dichloroethane (450 mL) and 5% platinum on carbon (16.9 g, 86.6 mmol) were added to a Parr vessel, which was placed under hydrogen pressure (30 psi, 2.1 x 10^5 Pa) and shaken until the reaction was complete. The reaction mixture was filtered and concentrated under reduced pressure. The residue was dissolved in ethyl acetate, and the resulting solution was filtered to remove an insoluble impurity, washed sequentially

with brine (3 x) and dilute aqueous sodium bicarbonate, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 42.52 g of *tert*-butyl 3-[(3-aminoquinolin-4-yl)amino]propylcarbamate.

Part C

Triethylamine (20.4 g, 202 mmol) was added to a solution of *tert*-butyl 3-[(3-aminoquinolin-4-yl)amino]propylcarbamate (42.52 g, 134.4 mmol) in dichloromethane (500 mL). Chloroacetyl chloride (16.7 g, 148 mmol) was added dropwise, and the reaction was stirred overnight at ambient temperature. The reaction mixture was filtered to remove a solid; the filtrate was concentrated under reduced pressure and mixed with ethyl acetate. The resulting mixture was filtered to remove a solid, washed sequentially with brine (3 x) and dilute aqueous sodium bicarbonate, concentrated under reduced pressure, and dried under high vacuum to provide 41.9 g of *tert*-butyl 3-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propylcarbamate.

Part D

A modification of the method described in Part D of Example 4 was used to treat *tert*-butyl 3-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propylcarbamate (36.76 g, 98.1 mmol) with potassium *tert*-butoxide (107.9 mL of a 1 M solution in THF). Following the work-up procedure, the product was mixed with ethyl acetate. The resulting mixture was filtered to remove a solid, and the filtrate was concentrated under reduced pressure to provide 30.0 g of *tert*-butyl 11,12-dihydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(10*H*)-carboxylate.

Part E

The general method described in Part E of Example 4 was used to treat *tert*-butyl 11,12-dihydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(10*H*)-carboxylate (30.0 g, 88.6 mmol) with mCPBA (23.8 g of 77% pure material, 138 mmol) to provide *tert*-butyl 5-oxido-11,12-dihydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(10*H*)-carboxylate. The product was not dried over magnesium sulfate but was dried under high vacuum overnight.

Part F

The general method described in Part F of Example 4 was used to aminate the material from Part E with ammonium hydroxide (170 mL) and *p*-toluenesulfonyl chloride (16.92 g, 88.74 mmol) to provide 28.44 g of *tert*-butyl 6-amino-11,12-dihydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(10*H*)-carboxylate.

Material from another run was purified by column chromatography on silica gel (eluting with dichloromethane:methanol in a gradient from 99:1 to 85:15) to provide the product as a white powder, mp 213°C.

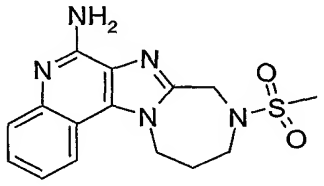
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, J = 8.1 Hz, 1H), 7.71 (d, J = 8.3 Hz, 1H), 7.39 (t, J = 7.8 Hz, 1H), 7.16 (t, J = 7.3 Hz, 1H), 5.68 (s, 2H), 4.71 (s, 2H), 4.60 (t, J = 5.2 Hz, 2H), 3.73-3.62 (m, 2H), 2.18-2.09 (m, 2H), 1.33 (s, 9H);

MS (APCI) *m/z* 354 $(M + H)^+$;

Anal. Calcd for $C_{19}H_{23}N_5O_2$: C, 64.57; H, 6.56; N, 19.82. Found: C, 64.29; H, 6.82; N, 19.54.

Example 7

9-(Methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine trifluoroacetate



Part A

The general method described in Part A of Example 5 was used to deprotect *tert*-butyl 6-amino-11,12-dihydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(10*H*)-carboxylate (28.44 g, 80.47 mmol). A precipitate was present at the end of the reaction and was isolated by filtration. The solid was dissolved in a small amount of water, precipitated with 1,4-dioxane, isolated by filtration, and dried for two days in a vacuum oven at 75 °C to provide 17.04 g of the 9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine hydrochloride.

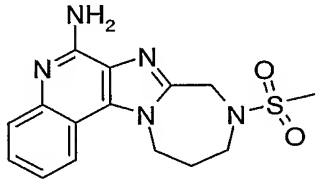
Part B

The general methods described in Part B of Example 5 were used to treat 9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine hydrochloride with triethylamine and methanesulfonyl chloride and purify the final product to provide 9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine trifluoroacetate, which was isolated as white needles, mp 250-250.9 °C.

Anal. Calcd for $C_{15}H_{17}N_5O_2S \bullet 1.10\ C_2HF_3O_2 \bullet 0.30\ H_2O$: C, 44.69; H, 4.08; N, 15.15. Found: C, 45.05; H, 3.76; N, 15.22.

Example 8

9-(Methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine



Part A

Potassium *tert*-butoxide (77.2 mL of a 1 M solution in THF) was added to a solution of *tert*-butyl 3-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propylcarbamate (24.12 g, 64.34 mmol, prepared according to the methods described in Example 6 Parts A through C) in THF (250 mL), and the reaction was stirred overnight at ambient temperature. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (eluting with 2N ammonia in methanol/dichloromethane in a gradient from 0:100 to 15:85) to provide 9.1 g of *tert*-butyl 11,12-dihydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(10*H*)-carboxylate.

Part B

Hydrogen chloride (100 mL of a 4 N solution in 1,4-dioxane) was added to a solution of *tert*-butyl 11,12-dihydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(10*H*)-carboxylate (9.1 g, 27 mmol) in methanol (60 mL). The reaction was stirred overnight at ambient temperature and then diluted with diethyl ether. A precipitate was

present and was isolated by filtration, washed sequentially with dichloromethane and diethyl ether, and dried under vacuum to provide 7.47 g of 9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline hydrochloride as a white solid.

Part C

Methanesulfonyl chloride (2.54 mL, 32.6 g) was added to a solution of 9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline hydrochloride (7.47 g, 27.2 mmol) and triethylamine (22.73 mL, 163.1 mmol) in DMF (50 mL). The reaction was stirred overnight at ambient temperature and then concentrated under reduced pressure to provide 3.065 g of 9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline.

Part D

mCPBA (2.55 g of 77%, 11.38 mmol) was added to a suspension of 9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline (3.0 g, 9.5 mmol) in chloroform, and the reaction was stirred for 30 minutes at ambient temperature. The reaction was incomplete as determined by LC/MS analysis. Additional mCPBA (approximately 0.5 equivalent) was added twice, and the reaction was stirred overnight. The solvent was removed under reduced pressure, and a solution of potassium hydroxide in methanol was added to adjust to pH 7.5. The methanol was removed under reduced pressure, and residue was dissolved in chloroform. Additional mCPBA (1.2 equivalents) was added, and the reaction was stirred for two hours. Additional mCPBA was added, and the reaction was stirred overnight at ambient temperature. Ammonium hydroxide (15 mL) and *p*-toluenesulfonyl chloride (1.99 g, 10.4 mmol) were added, and the reaction was stirred at ambient temperature for two hours. The organic layer was separated, concentrated under reduced pressure, and purified by normal phase preparative HPLC on silica gel (eluting with 2 N ammonia in methanol/chloroform in a 42-minute gradient from 0:100 to 25:75). The resulting solid was recrystallized from 5:2:1 acetonitrile/ethanol/methanol to provide 9-(methylsulfonyl)-5-oxido-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline, which was dissolved in chloroform, treated with ammonium hydroxide and *p*-toluenesulfonyl chloride, and purified by chromatography and recrystallization again as described above to provide 161

mg of 9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine as a white powder, mp 280°C.

^{1}H NMR (300 MHz, DMSO-d6) δ 8.27 (d, J = 7.5 Hz, 1H), 7.62 (d, J = 8.3 Hz, 1H), 7.44 (t, J = 8.1 Hz, 1H), 7.23 (t, J = 7.0 Hz, 1H), 6.63 (s, 2H), 4.91 (t, J = 4.6 Hz, 2H), 4.82 (s, 2H), 3.73 (t, J = 5.3 Hz, 2H), 2.79 (s, 3H), 2.25-2.16 (m, 2H);

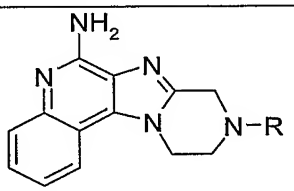
MS (APCI) *m/z* 332 $(M + H)^+$;

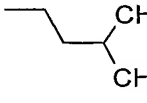
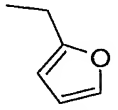
Anal. Calcd for $C_{15}H_{17}N_5O_2S$: C, 54.37; H, 5.17; N, 21.13. Found: C, 54.13; H, 4.96; N, 21.00.

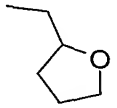
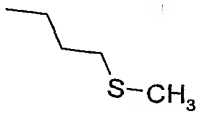
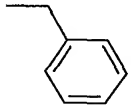
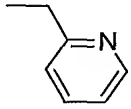
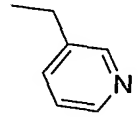
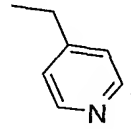
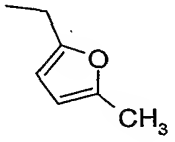
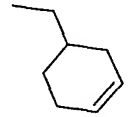
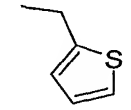
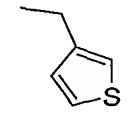
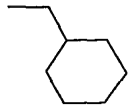
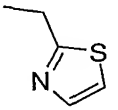
Examples 9-73

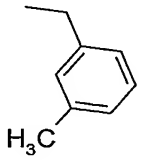
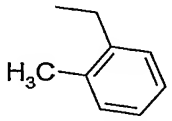
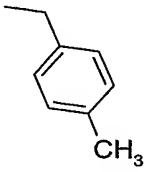
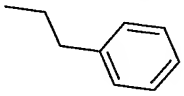
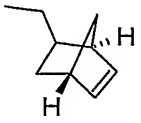
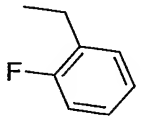
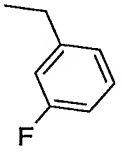
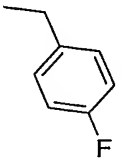
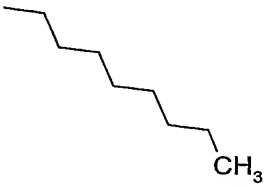
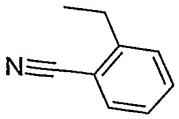
The aldehyde (0.125 mmol) indicated in the table below was added to a solution of 8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine hydrochloride (31.25 mg, 0.100 mmol) and *N,N*-diisopropylethylamine (0.035 mL, 0.20 mmol) in anhydrous DMF (2 mL) in a test tube. The test tube was capped and shaken for 15 minutes. Borane-pyridine complex (13 µL, 0.128 mmol) was added, and the reaction was shaken overnight. The solvent was removed by vacuum centrifugation. The compounds were purified by prep HPLC according to the method described above. The table below shows aldehyde used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

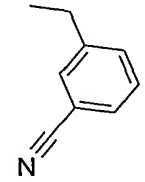
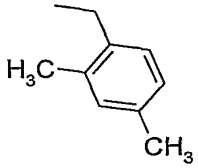
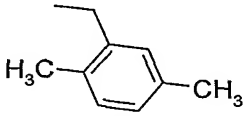
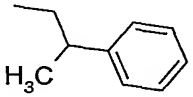
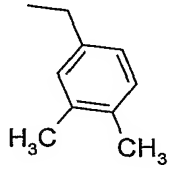
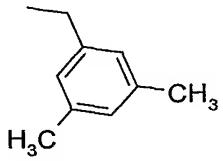
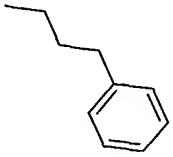
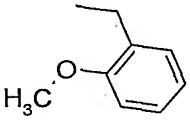
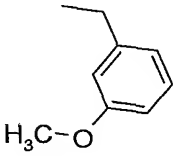
Examples 9-73

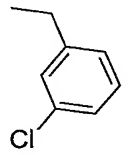
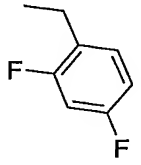
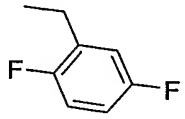
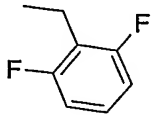
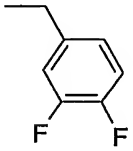
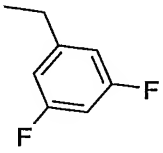
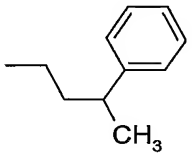
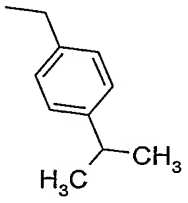


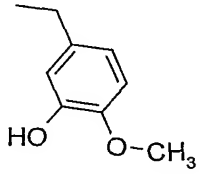
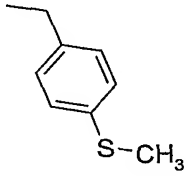
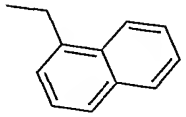
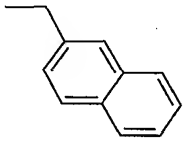
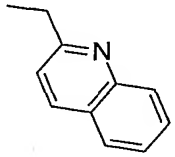
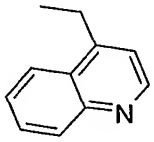
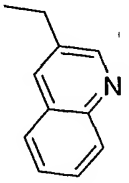
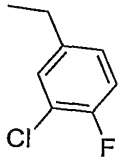
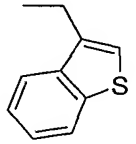
Example	Aldehyde	R	Measured Mass (M+H)
9	Isovaleraldehyde		310.2028
10	Furfural		320.1519

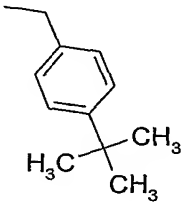
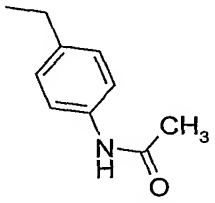
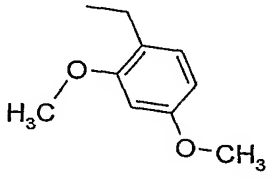
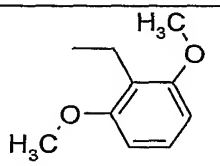
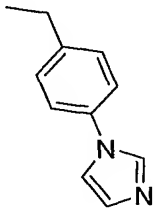
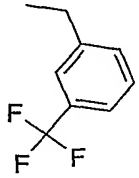
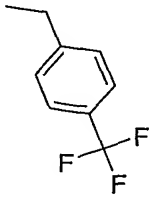
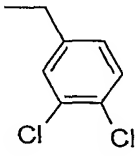
11	Tetrahydrofuran-3-carboxaldehyde		324.1843
12	3-(Methylthio)propionaldehyde		328.1619
13	Benzaldehyde		330.1751
14	2-Pyridinecarboxaldehyde		331.1684
15	3-Pyridinecarboxaldehyde		331.1691
16	4-Pyridinecarboxaldehyde		331.1670
17	5-Methylfurfural		334.1698
18	1,2,3,6-Tetrahydrobenzaldehyde		334.2045
19	2-Thiophenecarboxaldehyde		336.1305
20	3-Thiophenecarboxaldehyde		336.1279
21	Cyclohexanecarboxaldehyde		336.2178
22	Thiazole-2-carboxaldehyde		337.1244

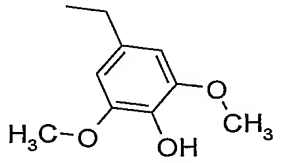
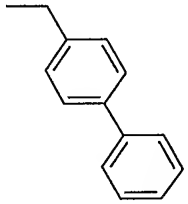
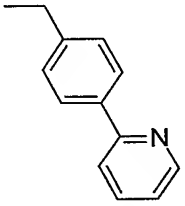
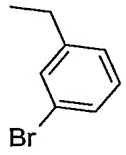
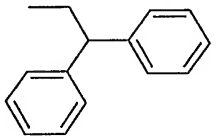
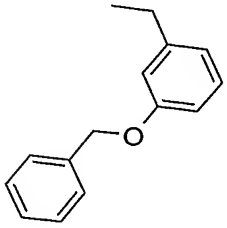
23	*m*-Tolualdehyde		344.1898
24	*o*-Tolualdehyde		344.1885
25	*p*-Tolualdehyde		344.1895
26	Phenylacetaldehyde		344.1908
27	5-Norbornene-2-carboxaldehyde		346.2049
28	2-Fluorobenzaldehyde		348.1633
29	3-Fluorobenzaldehyde		348.1656
30	4-Fluorobenzaldehyde		348.1638
31	Octanal		352.2493
32	2-Cyanobenzaldehyde		355.1696

33	3-Cyanobenzaldehyde		355.1700
34	2,4-Dimethylbenzaldehyde		358.2039
35	2,5-Dimethylbenzaldehyde		358.2057
36	2-Phenylpropionaldehyde		358.2044
37	3,4-Dimethylbenzaldehyde		358.2041
38	3,5-Dimethylbenzaldehyde		358.2042
39	3-Phenylpropionaldehyde		358.2040
40	2-Methoxybenzaldehyde		360.1855
41	3-Methoxybenzaldehyde		360.1830

42	3-Chlorobenzaldehyde		364.1318
43	2,3-Difluorobenzaldehyde		366.1544
44	2,4-Difluorobenzaldehyde		366.1559
45	2,5-Difluorobenzaldehyde		366.1544
46	2,6-Difluorobenzaldehyde		366.1552
47	3,4-Difluorobenzaldehyde		366.1526
48	3,5-Difluorobenzaldehyde		366.1559
49	3-Phenylbutyraldehyde		372.2213
50	Cuminaldehyde		372.2210

51	3-Hydroxy-4-methoxybenzaldehyde		376.1783
52	4-(Methylthio)benzaldehyde		376.1618
53	1-Naphthaldehyde		380.1891
54	2-Naphthaldehyde		380.1910
55	2-Quinolinecarboxaldehyde		381.1857
56	4-Quinolinecarboxaldehyde		381.1861
57	Quinoline-3-carboxaldehyde		381.1850
58	3-Chloro-4-fluorobenzaldehyde		382.1216
59	Thianaphthene-3-carboxaldehyde		386.1435

60	4-*tert*-Butylbenzaldehyde		386.2370
61	4-Acetamidobenzaldehyde		387.1960
62	2,4-Dimethoxybenzaldehyde		390.1944
63	2,6-Dimethoxybenzaldehyde		390.1940
64	4-(1*H*-Imidazol-1-yl)benzaldehyde		396.1953
65	3-(Trifluoromethyl)benzaldehyde		398.1613
66	4-(Trifluoromethyl)benzaldehyde		398.1630
67	3,4-Dichlorobenzaldehyde		398.0961

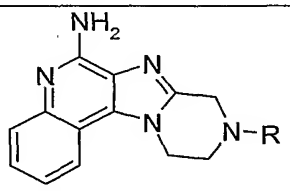
68	Syringaldehyde		406.1916
69	4-Biphenylcarboxaldehyde		406.2052
70	4-(2-Pyridyl)benzaldehyde		407.1984
71	3-Bromobenzaldehyde		408.0809
72	Diphenylacetaldehyde		420.2213
73	3-Benzyloxybenzaldehyde		436.2172

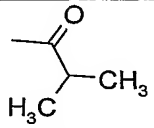
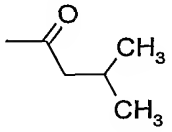
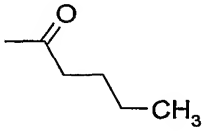
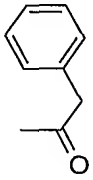
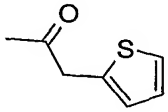
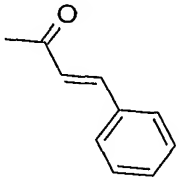
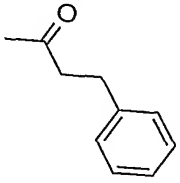
Examples 74-113

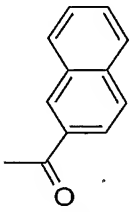
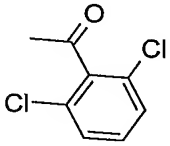
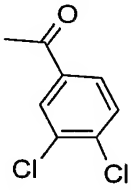
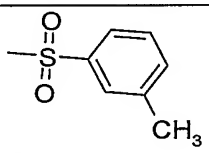
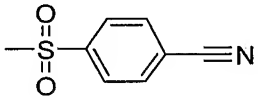
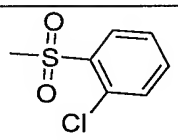
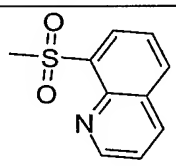
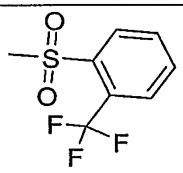
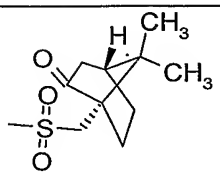
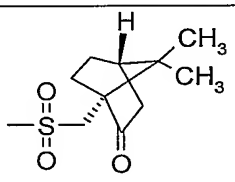
The reagent (0.11 mmol) indicated in the table below was added to a solution of 8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine hydrochloride (24 mg, 0.077 mmol) and *N,N*-diisopropylethylamine (0.070 mL, 0.40 mmol) in anhydrous DMF (2 mL) in a test tube. The test tube was capped and shaken overnight. One drop of deionized water was added to each test tube, and the solvent was removed by vacuum centrifugation. The compounds were purified by prep HPLC using the method described above. The table below shows the acid chloride, sulfonyl chloride, isocyanate, or

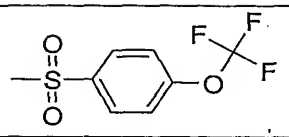
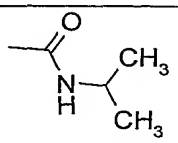
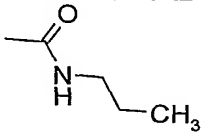
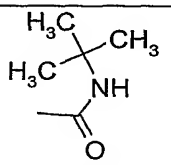
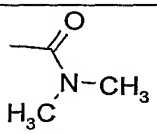
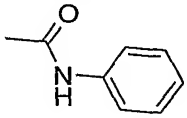
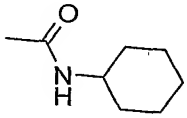
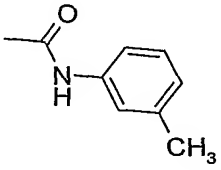
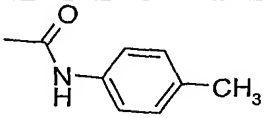
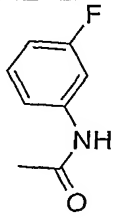
carbamoyl chloride used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

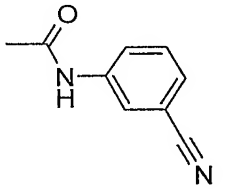
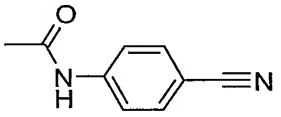
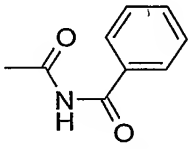
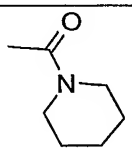
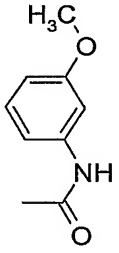
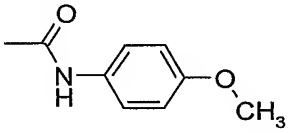
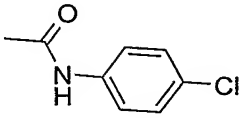
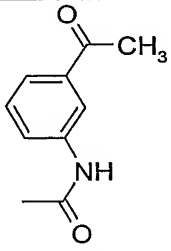
Examples 74-113

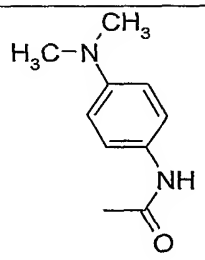
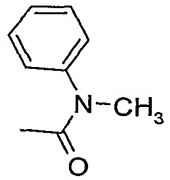
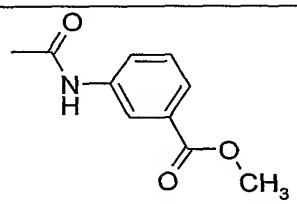
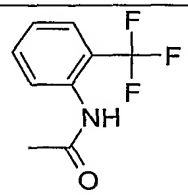
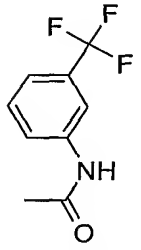


Example	Reagent	R	Measured Mass (M+H)
74	Isobutyryl chloride		310.1672
75	Isovaleryl chloride		324.1825
76	Pentanoyl chloride		324.1813
77	Phenylacetyl chloride		358.1682
78	Thiophene-2-acetyl chloride		364.2162
79	Cinnamoyl chloride		370.1676
80	Hydrocinnamoyl chloride		372.1840

81	2-Naphthoyl chloride		394.1695
82	2,6-Dichlorobenzoyl chloride		412.0770
83	3,4-Dichlorobenzoyl chloride		412.0736
84	*m*-Toluenesulfonyl chloride		394.1346
85	4-Cyanobenzenesulfonyl chloride		405.1173
86	2-Chlorobenzenesulfonyl chloride		414.0786
87	8-Quinolinesulfonyl chloride		431.1279
88	2-(Trifluoromethyl)benzenesulfonyl chloride		448.1073
89	(-)-Camphor-10-sulfonyl chloride		454.1919
90	D-(+)-10-Camphorsulfonyl chloride		454.1917

91	4-(Trifluoromethoxy) benzenesulfonyl chloride		464.1021
92	Isopropyl isocyanate		325.1791
93	*n*-Propyl isocyanate		325.1802
94	*tert*-Butyl isocyanate		339.1955
95	Dimethylcarbamoyl chloride		311.1600
96	Phenyl isocyanate		359.1635
97	Cyclohexane isocyanate		365.2094
98	*m*-Tolyl isocyanate		373.1790
99	*p*-Tolyl isocyanate		373.1812
100	3-Fluorophenyl isocyanate		377.1559

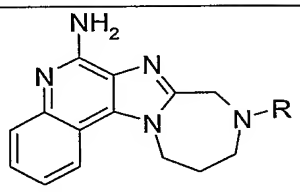
101	3-Cyanophenyl isocyanate		384.1573
102	4-Cyanophenyl isocyanate		384.1605
103	Benzoyl isocyanate		387.1575
104	1-Piperidinecarbonyl chloride		351.1909
105	3-Methoxyphenyl isocyanate		389.1732
106	4-Methoxyphenyl isocyanate		389.1761
107	4-Chlorophenyl isocyanate		393.1261
108	3-Acetylphenyl isocyanate		401.1763

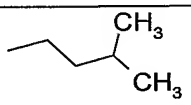
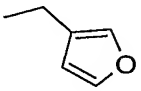
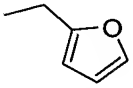
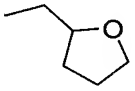
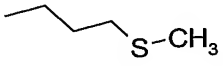
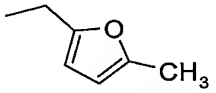
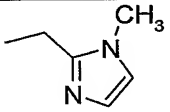
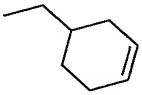
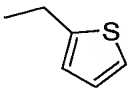
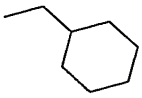
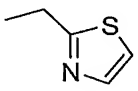
109	4-(Dimethylamino)phenyl isocyanate		402.2050
110	*N*-Methyl-*N*-phenylcarbamoyl chloride		373.1764
111	Methyl 3-isocyanatobenzoate		417.1692
112	2-(Trifluoromethyl)phenyl isocyanate		427.1511
113	3-(Trifluoromethyl)phenyl isocyanate		427.1479

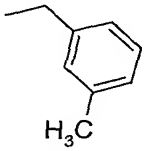
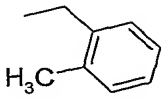
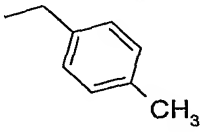
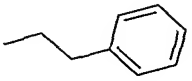
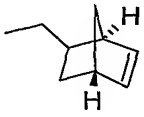
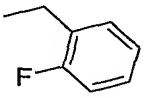
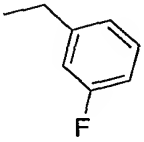
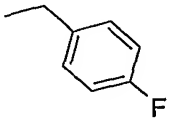
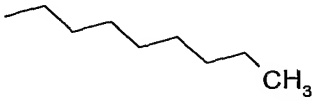
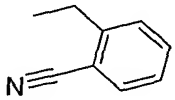
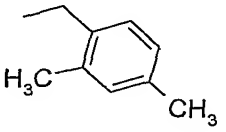
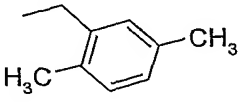
Examples 114-188

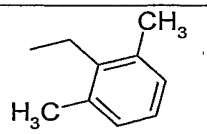
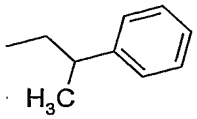
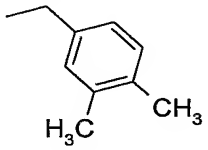
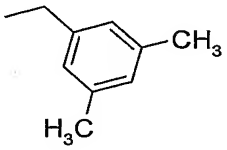
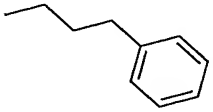
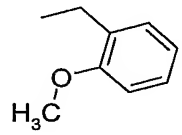
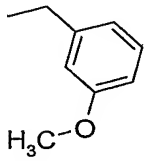
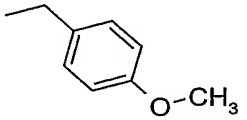
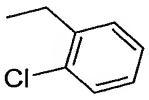
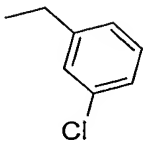
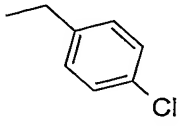
The general method described in Examples 8-73 was used to treat 9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine hydrochloride (32.3 mg, 0.099 mmol) with the aldehyde (0.125 mmol) indicated in the table below. The compounds were purified by prep HPLC using the method described above. The table below shows the aldehyde used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

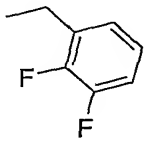
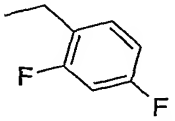
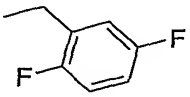
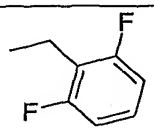
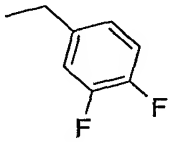
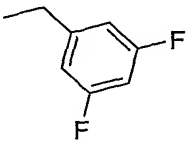
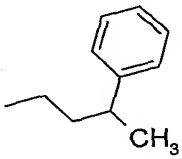
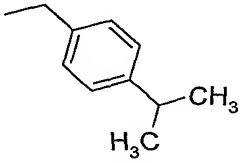
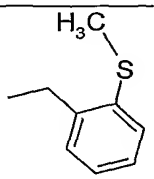
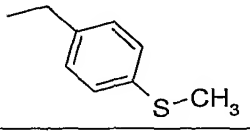
Examples 114-188

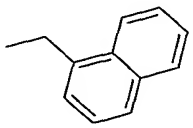
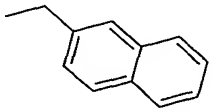
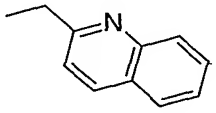
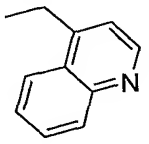
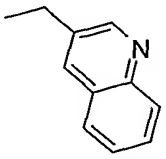
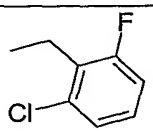
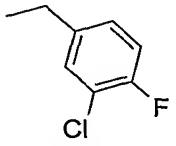
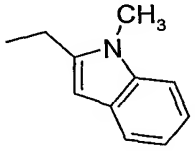
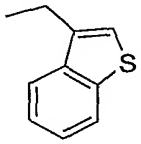
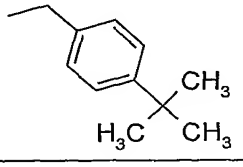


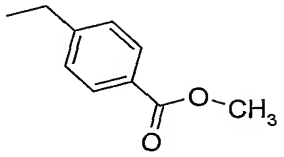
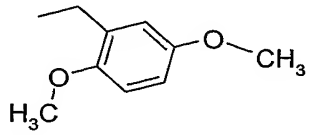
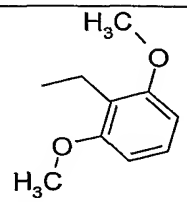
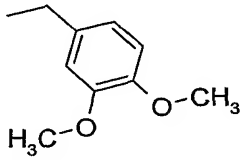
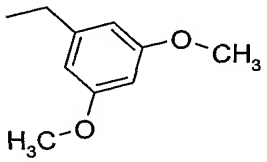
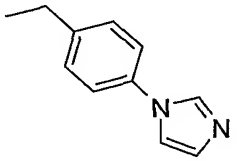
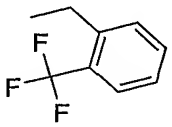
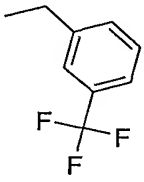
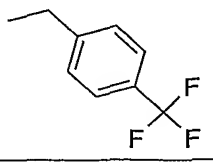
Example	Aldehyde	R	Measured Mass (M+H)
114	Isovaleraldehyde		324.2216
115	3-Furaldehyde		334.1687
116	Furfural		334.1680
117	Tetrahydrofuran-3-carboxaldehyde		338.2001
118	3-(Methylthio)propionaldehyde		342.1762
119	5-Methylfurfural		348.1849
120	1-Methyl-2-imidazolecarboxaldehyde		348.1934
121	1,2,3,6-Tetrahydrobenzaldehyde		348.2169
122	2-Thiophenecarboxaldehyde		350.1443
123	Cyclohexanecarboxaldehyde		350.2365
124	Thiazole-2-carboxaldehyde		351.1413

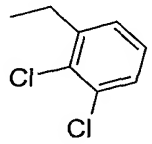
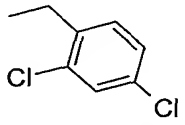
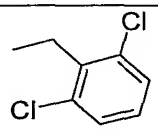
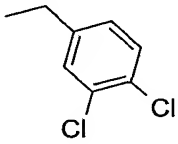
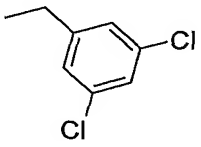
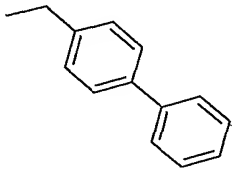
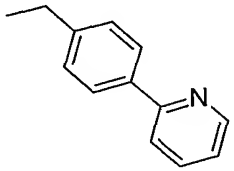
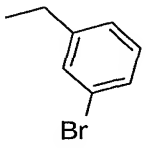
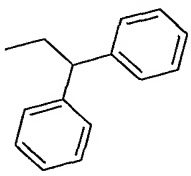
125	*m*-Tolualdehyde		358.2049
126	*o*-Tolualdehyde		358.2057
127	*p*-Tolualdehyde		358.2039
128	Phenylacetaldehyde		358.2029
129	5-Norbornene-2-carboxaldehyde		360.2199
130	2-Fluorobenzaldehyde		362.1790
131	3-Fluorobenzaldehyde		362.1784
132	4-Fluorobenzaldehyde		362.1775
133	Octanal		366.2640
134	2-Cyanobenzaldehyde		369.1852
135	2,4-Dimethylbenzaldehyde		372.2216
136	2,5-Dimethylbenzaldehyde		372.2185

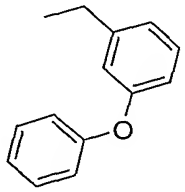
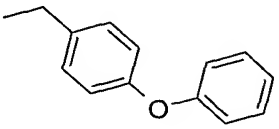
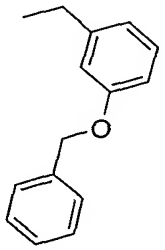
137	2,6-Dimethylbenzaldehyde		372.2202
138	2-Phenylpropionaldehyde		372.2208
139	3,4-Dimethylbenzaldehyde		372.2206
140	3,5-Dimethylbenzaldehyde		372.2205
141	3-Phenylpropionaldehyde		372.2208
142	2-Methoxybenzaldehyde		374.1985
143	3-Methoxybenzaldehyde		374.2007
144	*p*-Anisaldehyde		374.1991
145	2-Chlorobenzaldehyde		378.1490
146	3-Chlorobenzaldehyde		378.1509
147	4-Chlorobenzaldehyde		378.1519

148	2,3-Difluorobenzaldehyde		380.1683
149	2,4-Difluorobenzaldehyde		380.1696
150	2,5-Difluorobenzaldehyde		380.1691
151	2,6-Difluorobenzaldehyde		380.1713
152	3,4-Difluorobenzaldehyde		380.1695
153	3,5-Difluorobenzaldehyde		380.1693
154	3-Phenylbutyraldehyde		386.2366
155	Cuminaldehyde		386.2386
156	2-(Methylthio)benzaldehyde		390.1791
157	4-(Methylthio)benzaldehyde		390.1776

158	1-Naphthaldehyde		394.2055
159	2-Naphthaldehyde		394.2041
160	2-Quinolinecarboxaldehyde		395.2013
161	4-Quinolinecarboxaldehyde		395.2016
162	Quinoline-3-carboxaldehyde		395.2010
163	2-Chloro-6-fluorobenzaldehyde		396.1422
164	3-Chloro-4-fluorobenzaldehyde		396.1386
165	1-Methylindole-2-carboxaldehyde		397.2133
166	Thianaphthene-3-carboxaldehyde		400.1615
167	4-*tert*-Butylbenzaldehyde		400.2468

168	Methyl 4-formylbenzoate		402.1954
169	2,5-Dimethoxybenzaldehyde		404.2111
170	2,6-Dimethoxybenzaldehyde		404.2102
171	3,4-Dimethoxybenzaldehyde		404.2094
172	3,5-Dimethoxybenzaldehyde		404.2091
173	4-(1*H*-Imidazol-1-yl)benzaldehyde		410.2101
174	2-(Trifluoromethyl)benzaldehyde		412.1722
175	3-(Trifluoromethyl)benzaldehyde		412.1757
176	4-(Trifluoromethyl)benzaldehyde		412.1757

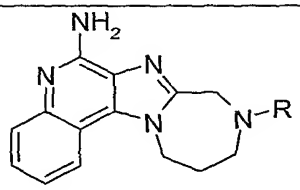
177	2,3-Dichlorobenzaldehyde		412.1117
178	2,4-Dichlorobenzaldehyde		412.1100
179	2,6-Dichlorobenzaldehyde		412.1117
180	3,4-Dichlorobenzaldehyde		412.1131
181	3,5-Dichlorobenzaldehyde		412.1116
182	4-Biphenylcarboxaldehyde		420.2209
183	4-(2-Pyridyl)benzaldehyde		421.2167
184	3-Bromobenzaldehyde		422.0999
185	Diphenylacetaldehyde		434.2369

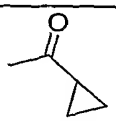
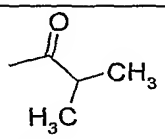
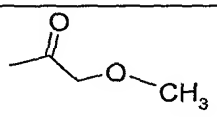
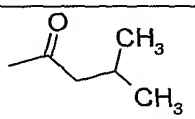
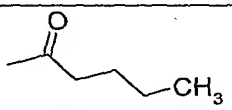
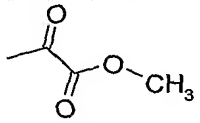
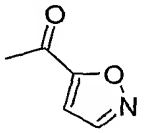
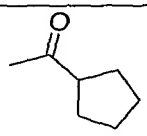
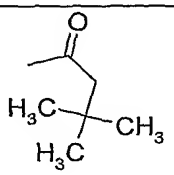
186	3-Phenoxybenzaldehyde		436.2137
187	4-Phenoxybenzaldehyde		436.2163
188	3-Benzyloxybenzaldehyde		450.2297

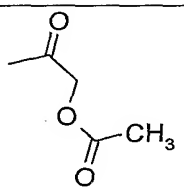
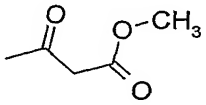
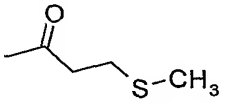
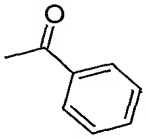
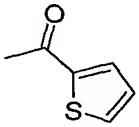
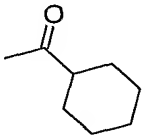
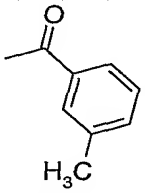
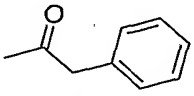
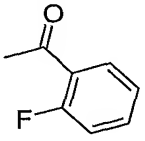
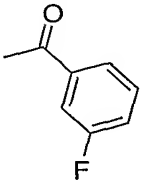
Example 189-329

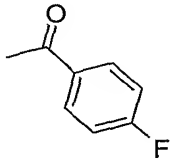
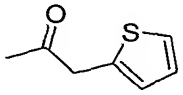
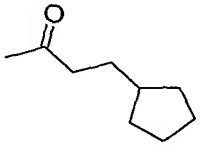
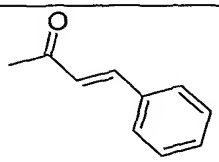
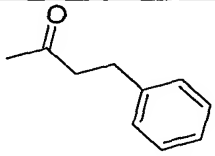
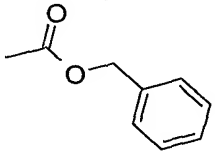
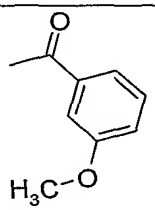
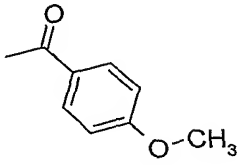
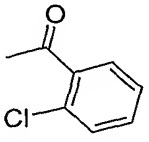
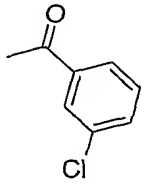
The general method described in Examples 74-113 was used to treat 9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine hydrochloride (32.5 mg, 0.100 mmol) with *N,N*-diisopropylethylamine (0.0525 mL, 0.30 mmol) and the reagent (0.108 mmol) indicated in the table below. The compounds were purified by prep HPLC using the method described above. The table below shows the acid chloride, sulfonyl chloride, isocyanate, carbamoyl chloride, or sulfamoyl chloride used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

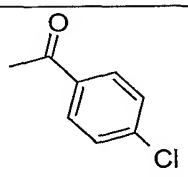
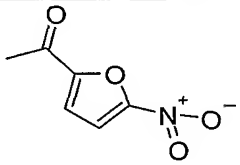
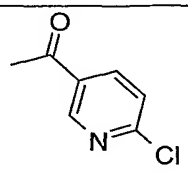
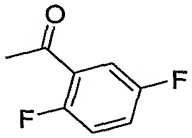
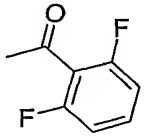
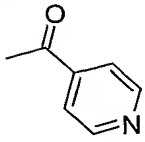
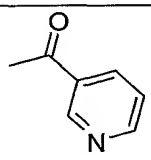
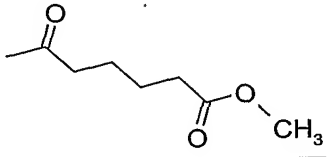
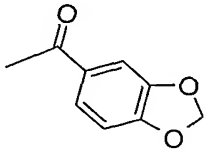
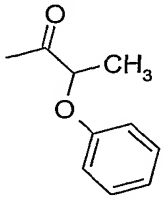
Examples 189-329

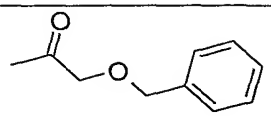
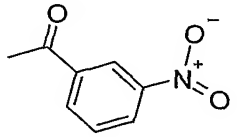
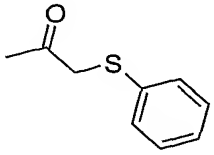
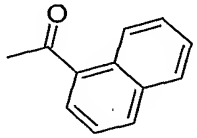
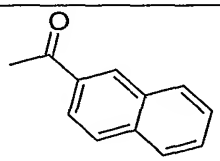
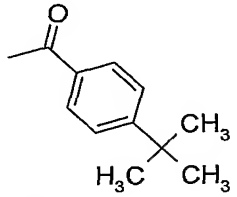
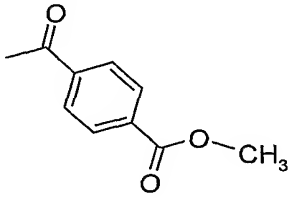
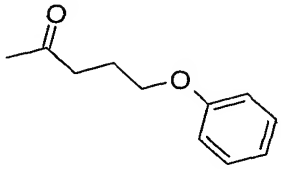
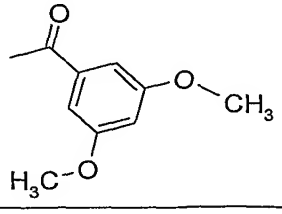


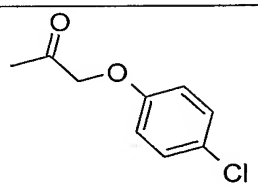
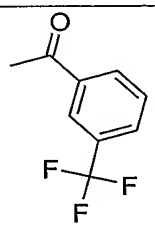
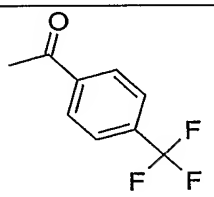
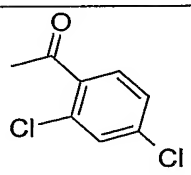
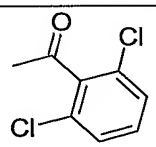
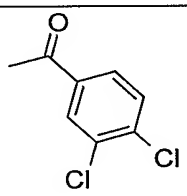
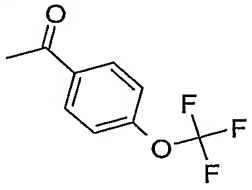
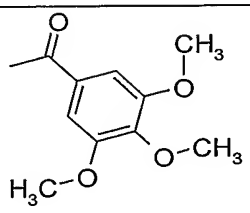
Example	Reagent	R	Measured Mass (M+H)
189	Cyclopropanecarbonyl chloride		322.1653
190	Isobutyryl chloride		324.1812
191	Methoxyacetyl chloride		326.1616
192	Isovaleryl chloride		338.1970
193	Pentanoyl chloride		338.1986
194	Methyl oxalyl chloride		340.1394
195	Isoxazole-5-carbonyl chloride		349.1419
196	Cyclopentanecarbonyl chloride		350.1971
197	*tert*-Butylacetyl chloride		352.2117

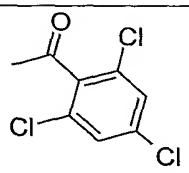
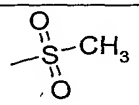
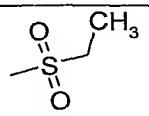
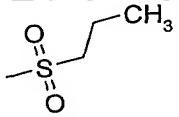
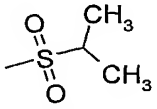
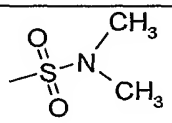
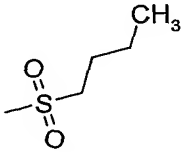
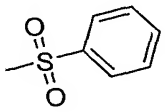
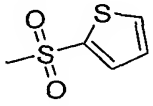
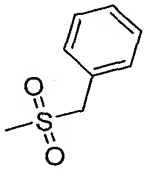
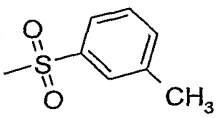
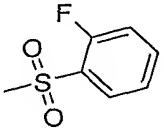
198	Acetoxyacetyl chloride		354.1550
199	Methyl malonyl chloride		354.1555
200	3-Methylthiopropionyl chloride		356.1541
201	Benzoyl chloride		358.1659
202	Thiophene-2-carbonyl chloride		364.1246
203	Cyclohexanecarbonyl chloride		364.2122
204	*m*-Toluoyl chloride		372.1835
205	Phenylacetyl chloride		372.1830
206	2-Fluorobenzoyl chloride		376.1570
207	3-Fluorobenzoyl chloride		376.1579

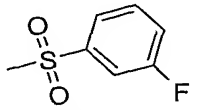
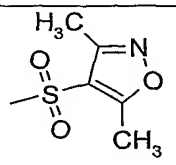
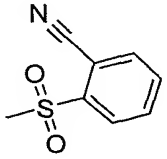
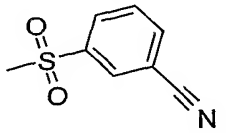
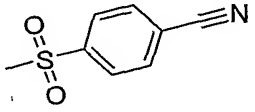
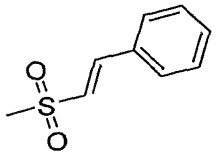
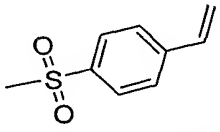
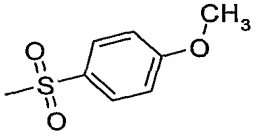
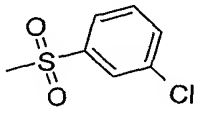
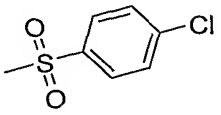
208	4-Fluorobenzoyl chloride		376.1573
209	2-Thiopheneacetyl chloride		378.1382
210	3-Cyclopentylpropionyl chloride		378.2298
211	Cinnamoyl chloride		384.1814
212	Hydrocinnamoyl chloride		386.1988
213	Benzyl chloroformate		388.1793
214	*m*-Anisoyl chloride		388.1752
215	*p*-Anisoyl chloride		388.1808
216	2-Chlorobenzoyl chloride		392.1268
217	3-Chlorobenzoyl chloride		392.1276

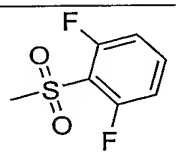
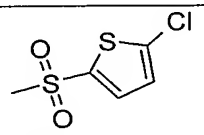
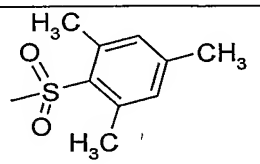
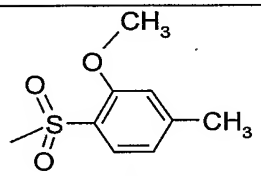
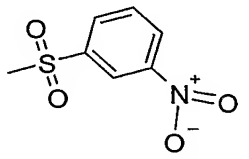
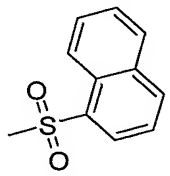
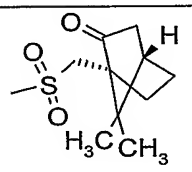
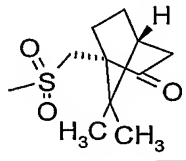
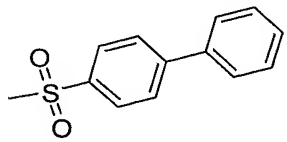
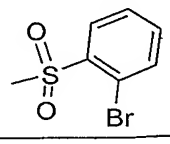
218	4-Chlorobenzoyl chloride		392.1291
219	5-Nitro-2-furoyl chloride		393.1317
220	6-Chloronicotinyl chloride		393.1237
221	2,5-Difluorobenzoyl chloride		394.1472
222	2,6-Difluorobenzoyl chloride		394.1468
223	Isonicotinoyl chloride hydrochloride		359.1619
224	Nicotinoyl chloride hydrochloride		359.1613
225	Methyl adipoyl chloride		396.2035
226	3,4-Methylenedioxybenzoyl chloride		402.1560
227	2-Phenoxypropionyl chloride		402.1921

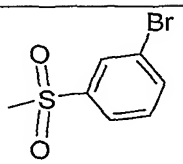
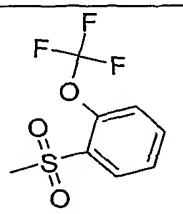
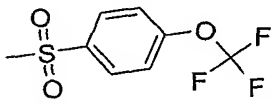
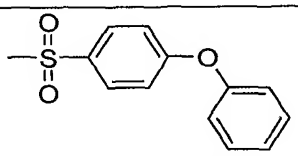
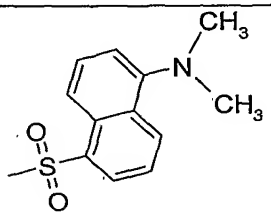
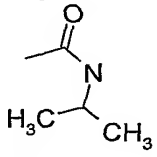
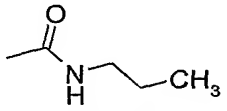
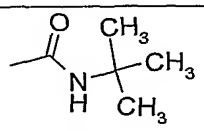
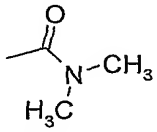
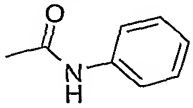
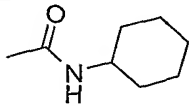
228	Benzyloxyacetyl chloride		402.1928
229	3-Nitrobenzoyl chloride		403.1527
230	(Phenylthio)acetyl chloride		404.1550
231	1-Naphthoyl chloride		408.1833
232	2-Naphthoyl chloride		408.1820
233	4-*tert*-Butylbenzoyl chloride		414.2271
234	Methyl 4-chlorocarbonyl benzoate		416.1727
235	4-Phenoxybutyryl chloride		416.2069
236	3,5-Dimethoxybenzoyl chloride		418.1880

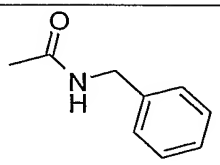
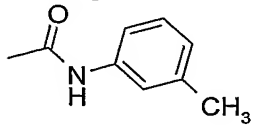
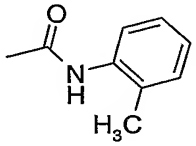
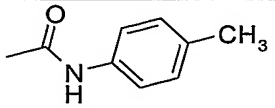
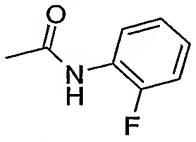
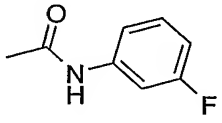
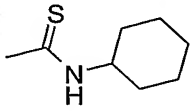
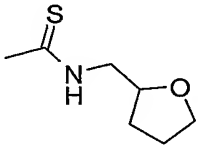
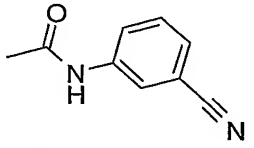
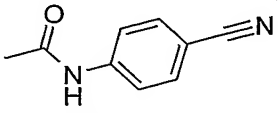
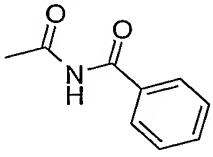
237	4-Chlorophenoxyacetyl chloride		422.1409
238	3-(Trifluoromethyl)benzoyl chloride		426.1581
239	4-(Trifluoromethyl)benzoyl chloride		426.1558
240	2,4-Dichlorobenzoyl chloride		426.0907
241	2,6-Dichlorobenzoyl chloride		426.0891
242	3,4-Dichlorobenzoyl chloride		426.0871
243	4-(Trifluoromethoxy)benzoyl chloride		442.1489
244	3,4,5-Trimethoxybenzoyl chloride		448.2001

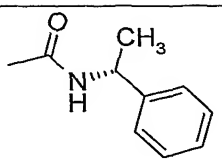
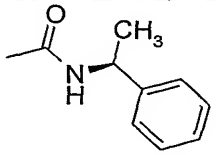
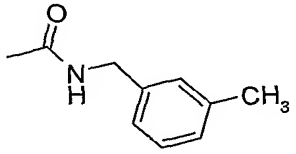
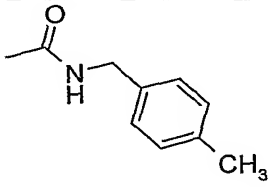
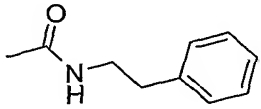
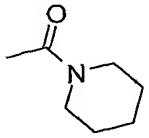
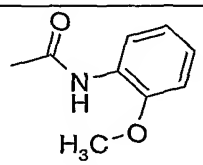
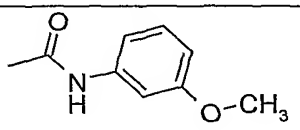
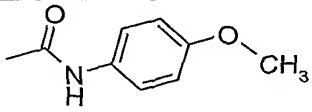
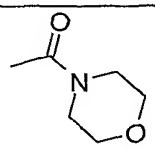
245	2,4,6-Trichlorobenzoyl chloride		460.0494
246	Methanesulfonyl chloride		332.1168
247	Ethanesulfonyl chloride		346.1333
248	1-Propanesulfonyl chloride		360.1497
249	Isopropylsulfonyl chloride		360.1490
250	Dimethylsulfamoyl chloride		361.1455
251	1-Butanesulfonyl chloride		374.1654
252	Benzenesulfonyl chloride		394.1320
253	2-Thiophenesulfonyl chloride		400.0913
254	α-Toluenesulfonyl chloride		408.1497
255	*m*-Toluenesulfonyl chloride		408.1502
256	2-Fluorobenzenesulfonyl chloride		412.1233

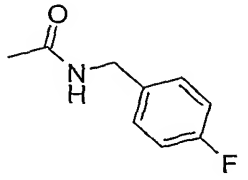
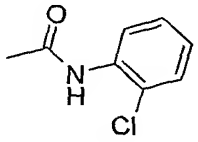
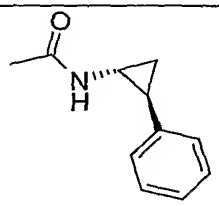
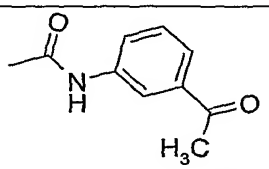
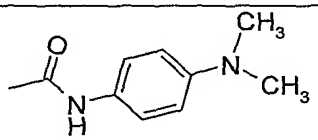
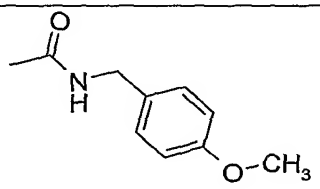
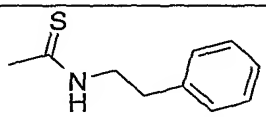
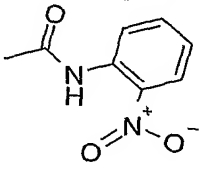
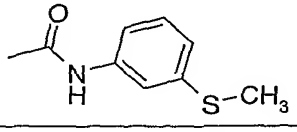
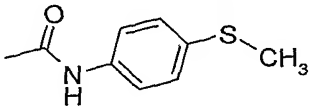
257	3-Fluorobenzenesulfonyl chloride		412.1238
258	3,5-Dimethylisoxazole-4-sulfonyl chloride		413.1385
259	2-Cyanobenzenesulfonyl chloride		419.1289
260	3-Cyanobenzenesulfonyl chloride		419.1307
261	4-Cyanobenzenesulfonyl chloride		419.1302
262	β-Styrenesulfonyl chloride		420.1479
263	*p*-Styrenesulfonyl chloride		420.1496
264	4-Methoxybenzenesulfonyl chloride		424.1448
265	3-Chlorobenzenesulfonyl chloride		428.0941
266	4-Chlorobenzenesulfonyl chloride		428.0944
267	2,4-Difluorobenzenesulfonyl chloride		430.1145

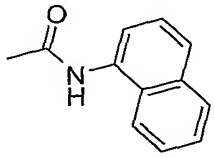
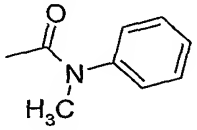
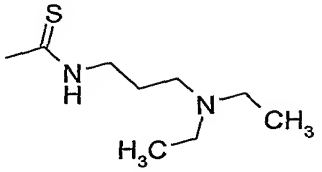
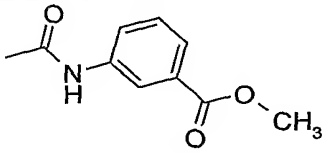
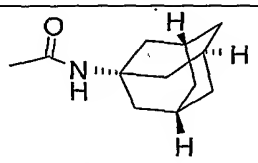
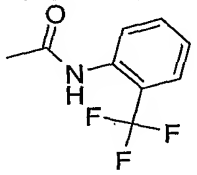
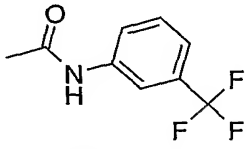
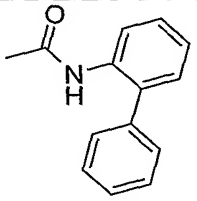
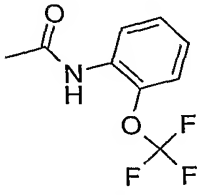
268	2,6-Difluorobenzenesulfonyl chloride		430.1121
269	5-Chlorothiophene-2-sulfonyl chloride		434.0519
270	2-Mesitylenesulfonyl chloride		436.1814
271	2-Methoxy-4-methylbenzenesulfonyl chloride		438.1613
272	3-Nitrobenzenesulfonyl chloride		439.1199
273	1-Naphthalenesulfonyl chloride		444.1506
274	(-)-Camphor-10-sulfonyl chloride		468.2098
275	D-(+)-10-Camphorsulfonyl chloride		468.2106
276	4-Biphenylsulfonyl chloride		470.1639
277	2-Bromobenzenesulfonyl chloride		472.0459

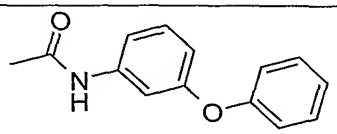
278	3-Bromobenzenesulfonyl chloride		472.0471
279	2-(Trifluoromethoxy) benzenesulfonyl chloride		478.1171
280	4-(Trifluoromethoxy) benzenesulfonyl chloride		478.1155
281	4-Phenoxybenzenesulfonyl chloride		486.1613
282	Dansyl chloride		487.1920
283	Isopropyl isocyanate		339.1965
284	*n*-Propyl isocyanate		339.1947
285	*tert*-Butyl isocyanate		353.2108
286	Dimethylcarbamoyl chloride		325.1804
287	Phenyl isocyanate		373.1803
288	Cyclohexane isocyanate		379.2275

289	Benzyl isocyanate		387.1943
290	*m*-Tolyl isocyanate		387.1951
291	*o*-Tolyl isocyanate		387.1937
292	*p*-Tolyl isocyanate		387.1959
293	2-Fluorophenyl isocyanate		391.1706
294	3-Fluorophenyl isocyanate		391.1705
295	Cyclohexyl isothiocyanate		395.2041
296	2-Tetrahydrofurfuryl isothiocyanate		397.1836
297	3-Cyanophenyl isocyanate		398.1749
298	4-Cyanophenyl isocyanate		398.1752
299	Benzoyl isocyanate		401.1750

300	(R)-(+)-1-Phenylethyl isocyanate		401.2080
301	(S)-(-)-1-Phenylethyl isocyanate		401.2078
302	3-Methylbenzyl isocyanate		401.2122
303	4-Methylbenzyl isocyanate		401.2096
304	Phenethyl isocyanate		401.2127
305	1-Piperidinecarbonyl chloride		365.2122
306	2-Methoxyphenyl isocyanate		403.1877
307	3-Methoxyphenyl isocyanate		403.1902
308	4-Methoxyphenyl isocyanate		403.1908
309	Morpholine-4-carbonyl chloride		367.1911

310	4-Fluorobenzyl isocyanate		405.1851
311	2-Chlorophenyl isocyanate		407.1408
312	*trans*-2-Phenylcyclopropyl isocyanate		413.2106
313	3-Acetylphenyl isocyanate		415.1899
314	4-(Dimethylamino)phenyl isocyanate		416.2213
315	4-Methoxybenzyl isocyanate		417.2069
316	Phenethyl isothiocyanate		417.1895
317	2-Nitrophenyl isocyanate		418.1662
318	3-(Methylthio)phenyl isocyanate		419.1671
319	4-(Methylthio)phenyl isocyanate		419.1695

320	1-Naphthyl isocyanate		423.1969
321	*N*-Methyl-*N*-phenylcarbamoyl chloride		387.1961
322	3-(Diethylamino)propyl isothiocyanate		426.2465
323	Methyl 3-isocyanatobenzoate		431.1852
324	1-Adamantyl isocyanate		431.2549
325	2-(Trifluoromethyl)phenyl isocyanate		441.1647
326	3-(Trifluoromethyl)phenyl isocyanate		441.1679
327	2-Biphenylyl isocyanate		449.2090
328	2-(Trifluoromethoxy)phenyl isocyanate		457.1633

329	3-Phenoxyphenyl isocyanate		465.2073

Examples 330-362

Part A

mCPBA (3.89 g of 77% pure material, 17.36 mmol) was added to a solution of *tert*-butyl 11-{[*tert*-butyl(dimethyl)silyl]oxy}-11,12-dihydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(10*H*)-carboxylate (4.07 g, 8.68 mol) in chloroform, and the reaction was stirred for 30 minutes at ambient temperature. Additional mCPBA (0.5 equivalent) was added, and the reaction was stirred for four hours. Ammonium hydroxide (50 mL) was added with vigorous stirring, and after ten minutes, *p*-toluenesulfonyl chloride (1.82 g, 9.55 mmol) was added. The reaction was stirred overnight at ambient temperature and then concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluting sequentially with 98.5:1:0.5 and 89:10:1 dichloromethane:methanol:ammonium hydroxide), and the resulting product was dried under high vacuum to provide 2.25 g of *tert*-butyl 6-amino-11-{[*tert*-butyl(dimethyl)silyl]oxy}-11,12-dihydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(10*H*)-carboxylate.

Part B

Hydrochloric acid (75 mL of a 4 N solution in 1,4-dioxane) was added to *tert*-butyl 6-amino-11-{[*tert*-butyl(dimethyl)silyl]oxy}-11,12-dihydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(10*H*)-carboxylate (2.15 g, 4.45 mmol), and the reaction was stirred for four hours at ambient temperature and then concentrated under reduced pressure. The residue was washed with dichloromethane and dried overnight under high vacuum to provide 930 mg of 11-{[*tert*-butyl(dimethyl)silyl]oxy}-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine hydrochloride as a light brown powder.

Part C

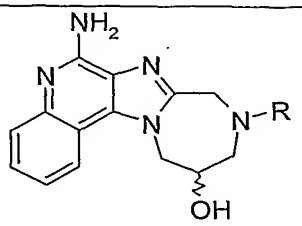
The reagent (0.11 mmol) indicated in the table below was added to a solution of 11-{[*tert*-butyl(dimethyl)silyl]oxy}-9,10,11,12-tetrahydro-8*H*-

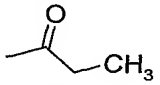
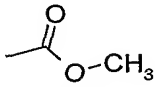
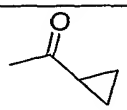
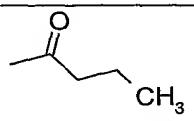
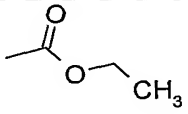
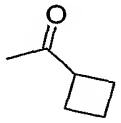
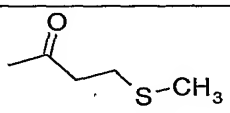
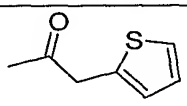
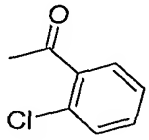
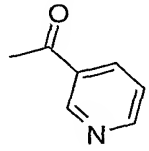
[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine hydrochloride (24 mg, 0.077 mmol) and *N,N*-diisopropylethylamine (0.0225 mL, 0.13 mmol) in chloroform (1 mL) in a test tube. For Examples 330-348, the test tube was capped and shaken overnight at ambient temperature. For Examples 349-362, the test tube was capped, heated at 50 °C for four hours, and then shaken overnight at ambient temperature. The reaction mixtures were separated by solid-supported liquid-liquid extraction according to the following procedure. Each reaction was loaded onto diatomaceous earth that had been treated with 600 μL of 1 N sodium hydroxide for 20 minutes. After ten minutes, chloroform (500 μL) was added to elute the product from the diatomaceous earth into a well of a microtitre plate. After an additional 15 minutes, the process was repeated with additional chloroform (500 μL). The solvent was then removed by vacuum centrifugation.

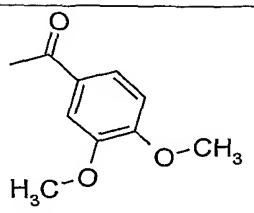
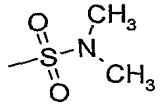
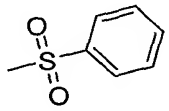
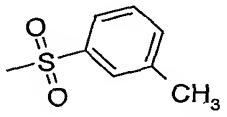
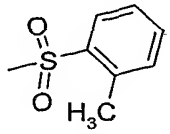
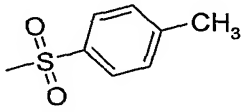
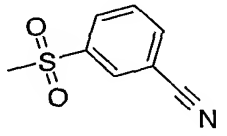
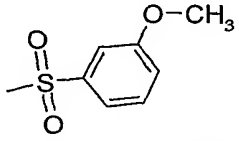
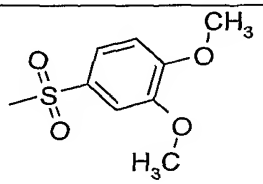
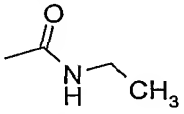
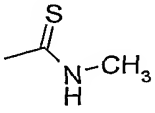
Part D

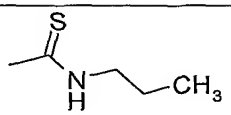
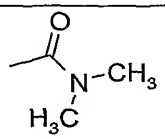
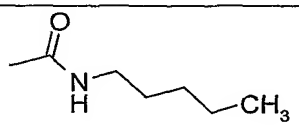
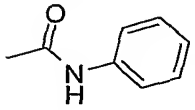
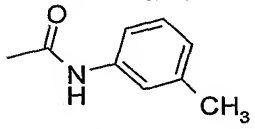
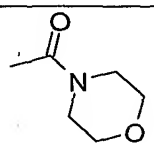
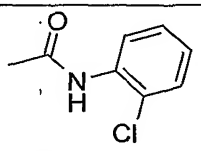
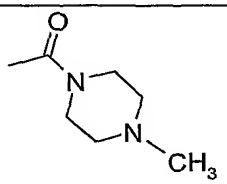
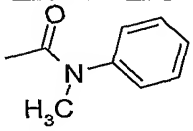
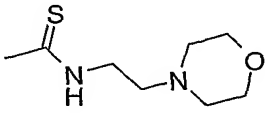
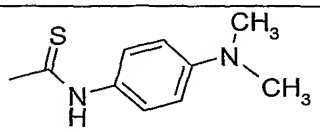
THF (1 mL) was added to each product from Part C located in a well of the microtitre plate described in Part C. The wells were capped and shaken until the mixture became homogeneous. The solutions were cooled to -20 °C, and tetrabutylammonium fluoride (300 μL of a 1.0 M solution in THF) was added. The plate was shaken, returned to the cold bath, and then allowed to warm to ambient temperature overnight. Trifluoroacetic acid (25 μL) was added to each well, and the plate was shaken carefully. The volatiles were then removed by vacuum centrifugation. Some of the compounds were purified by prep HPLC using the method described above. Other compounds were purified using a Waters OASIS Sample Extractions Cartridge MCX (5 cc) according to the following procedure prior to purification by prep HPLC. The sample was dissolved in methanol (2 mL) and passed through the cartridge. The cartridge was washed with methanol (2 x 2 mL) and transferred to a clean test tube. A solution of 7 N ammonia in methanol (3 x 2 mL) was then passed through the cartridge, and the basic solution was collected and concentrated. The table below shows the acid chloride, sulfonyl chloride, isocyanate, carbamoyl chloride, or sulfamoyl chloride used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

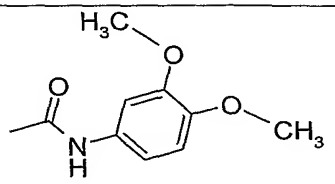
Examples 330-362



Example	Reagent	R	Measured Mass (M+H)
330	Propionyl chloride		326.1619
331	Methyl chloroformate		328.1409
332	Cyclopropanecarbonyl chloride		338.1617
333	Butyryl chloride		340.1750
334	Ethyl chloroformate		342.1549
335	Cyclobutanecarbonyl chloride		352.1789
336	3-Methylthiopropionyl chloride		372.1496
337	2-Thiopheneacetyl chloride		394.1355
338	2-Chlorobenzoyl chloride		408.1212
339	Nicotinoyl chloride hydrochloride		375.1569

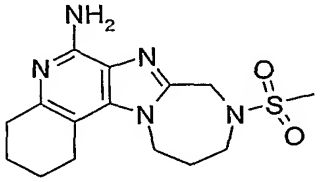
340	3,4-Dimethoxybenzoyl chloride		434.1830
341	Dimethylsulfamoyl chloride		377.1381
342	Benzenesulfonyl chloride		410.1275
343	3-Methylbenzenesulfonyl chloride		424.1437
344	*o*-Toluenesulfonyl chloride		424.1450
345	*p*-Toluenesulfonyl chloride		424.1442
346	3-Cyanobenzenesulfonyl chloride		435.1243
347	3-Methoxybenzenesulfonyl chloride		440.1366
348	3,4-Dimethoxybenzenesulfonyl chloride		470.1510
349	Ethyl isocyanate		341.1724
350	Methyl isothiocyanate		343.1343

351	*n*-Propyl isothiocyanate		371.1641
352	*N,N*-Dimethylcarbamoyl chloride		341.1729
353	Pentyl isocyanate		383.2206
354	Phenyl isocyanate		389.1733
355	*m*-Tolyl isocyanate		403.1882
356	4-Morpholinecarbonyl chloride		383.1808
357	2-Chlorophenyl isocyanate		423.1343
358	4-Methyl-1-piperazinecarbonyl chloride		396.2111
359	*N*-Methyl-*N*-phenylcarbamoyl chloride		403.1892
360	2-Morpholinoethyl isothiocyanate		442.2038
361	4-(Dimethylamino)phenyl isothiocyanate		448.1911

362	3,4-Dimethoxyphenyl isocyanate		449.1924

Example 363

9-(Methylsulfonyl)-2,3,4,8,9,10,11,12-octahydro-1*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine



Part A

Triethylamine (2.32 mL, 16.7 mmol) was added to a suspension of 9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine hydrochloride (1.61 g, 5.56 mmol, Example 7 Part A) in DMF (20 mL). The mixture was sonicated for ten minutes at 80 °C, and methanesulfonyl chloride (764 mg, 6.67 mmol) was slowly added. The mixture was stirred at ambient temperature overnight. The solvent was removed under reduced pressure. Unsuccessful attempts were made to purify the product, and ultimately, the product was isolated by filtration to provide 894 mg of 9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine containing some impurities.

Part B

Platinum (II) oxide (613.14 mg, 2.7 mmol) was added to a Parr vessel containing the material from Part A and trifluoroacetic acid (20 mL), and the reaction was placed under hydrogen pressure (50 psi, 3.4 x 10^5 Pa) overnight. The trifluoroacetic acid was then removed under reduced pressure, and the residue was mixed with methanol and filtered. The filtrate was concentrated under reduced pressure, and the residue was stirred with hydrogen chloride (20 mL of a 4 N solution in 1,4-dioxane) for ten minutes. The mixture was filtered, and the filtrate was concentrated under reduced pressure. A solution of 0.5 M potassium hydroxide in methanol was added to the residue until the mixture was

pH 13, and the mixture was stirred for 15 minutes. The solvent was removed under reduced pressure, and the residue was dissolved in chloroform. The resulting solution was washed sequentially with 10% aqueous sodium carbonate, 2 N aqueous sodium hydroxide, and brine and then concentrated under reduced pressure. The residue was purified by column chromatography on a COMBIFLASH system (available from Isco, Inc., Lincoln, Nebraska, USA) (eluting with a gradient of 1-10% methanol in dichloromethane) followed by recrystallization from acetonitrile. The crystals were dried overnight in a vacuum oven at 65 °C to provide 9-(methylsulfonyl)-2,3,4,8,9,10,11,12-octahydro-1*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine as a white powder, mp 270-272 °C.

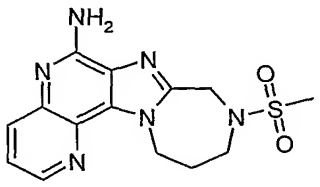
^{1}H NMR (300 MHz, DMSO-D6) δ 5.85 (s, 2H), 4.69 (s, 2H), 4.56 (t, J = 3.9 Hz, 2H), 3.65 (t, J = 6.0 Hz, 2H), 2.94 (t, J = 7.5 Hz, 2H), 2.73 (s, 3H), 2.65 (m, 2H), 2.07 (m, 2H), 1.75 (m, 4H);

MS (APCI) *m/z* 336 $(M + H)^+$;

Anal. Calcd for $C_{15}H_{21}N_5O_2S \bullet 0.30\ H_2O$: C, 52.86; H, 6.39; N, 20.55. Found: C, 53.05; H, 6.07; N, 20.20.

Example 364

9-(Methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*][1,5]naphthyridin-6-amine



Part A

Phosphorus oxychloride (31.7 mL, 340 mmol) was added dropwise to a stirred suspension of 3-nitro[1,5]naphthyridine-4-ol (50.0 g, 262 mmol) in 350 mL of DMF that was cooled with a water bath surrounding the reaction vessel. The resulting green suspension was stirred at ambient temperature for 5 hours and poured into 1.5 L of ice water and stirred for an additional hour. The suspension was filtered, washed with water (3 x 150 mL), and the resulting orange filter cake was dissolved in dichloromethane (800 mL) and washed with saturated aqueous sodium bicarbonate. The layers were separated

and the organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford 50.49 g of 4-chloro-3-nitro[1,5]naphthyridine as an orange solid.

Part B

Di-*tert*-butyl dicarbonate (45.0 g, 206 mmol) was dissolved in 200 mL of THF and added via an addition funnel to a solution of 1,3-diaminopropane (51.6 mL, 618 mmol) in 100 mL of THF. The internal temperature of the reaction mixture was maintained below 8° C. After addition was complete, the reaction mixture was allowed to warm to ambient temperature and stirred overnight. The resulting mixture was diluted with 250 mL of water and 400 mL of ethyl acetate and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were concentrated under reduced pressure and the remaining material was diluted in 800 mL of water. The pH of the combined aqueous layers was adjusted to pH 4 by the addition of 2M hydrochloric acid. The solution was extracted with dichloromethane (3 x 200 mL). The pH of the aqueous solution was adjusted to 12 using a 2M solution of sodium hydroxide and extracted with dichloromethane (6 x 150 mL). The combined organic layers from the final set of extractions were washed with brine (300 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford 25.01 g of *tert*-butyl 3-aminopropylcarbamate as a colorless oil.

Part C

A solution of *tert*-butyl 3-aminopropylcarbamate (15.7 g, 90.2 mmol) in dichloromethane (50 mL) was added dropwise over 30 minutes to a solution of 4-chloro-3-nitro[1,5]naphthyridine (18.0 g, 85.9 mmol) and triethylamine (15.6 mL, 112 mmol) in dichloromethane (235 mL) at room temperature. The reaction mixture was stirred for 2.5 hours and then concentrated under reduced pressure to afford an orange solid. Water (300 mL) was added and the mixture was stirred for one hour. The solid was isolated by filtration, washed with water (3 x 50 mL), and dried under vacuum at 70 °C to afford 29.5 g of *tert*-butyl 3-[(3-nitro[1,5]naphthyridin-4-yl)amino]propylcarbamate as a yellow solid.

Part D

A mixture of *tert*-butyl 3-[(3-nitro[1,5]naphthyridin-4-yl)amino]propylcarbamate (20.0 g, 57.6 mmol), 5% platinum on carbon, and ethyl acetate was hydrogenated on a Parr apparatus for two hours at 30 psi (2.1 x 10^5 Pa). The mixture was filtered through CELITE filter agent, which was rinsed afterwards with ethyl acetate (150 mL). The filtrate was concentrated to afford *tert*-butyl 3-[(3-amino[1,5]naphthyridin-4-yl)amino]propylcarbamate as a yellow foam, all of which was used in the next step.

Part E

Chloroacetyl chloride (5.00 mL, 63.4 mmol) was added dropwise to a 0 °C solution of *tert*-butyl 3-[(3-amino[1,5]naphthyridin-4-yl)amino]propylcarbamate (from Part D, approximately 57.6 mmol) in dichloromethane (230 mL). The reaction was allowed to warm to room temperature and was stirred for 1 hour. The solvent was removed under reduced pressure to afford *tert*-butyl 3-({3-[(chloroacetyl)amino][1,5]naphthyridin-4-yl}amino)propylcarbamate hydrochloride as a solid, all of which was used in the next step.

Part F

To a solution of *tert*-butyl 3-({3-[(chloroacetyl)amino][1,5]naphthyridin-4-yl}amino)propylcarbamate hydrochloride (from Part E, approximately 57.6 mmol) in 3:1 ethanol/water (240 mL) was added 6 M aqueous potassium carbonate. The reaction mixture was stirred at room temperature for 1 hour, 40 °C for 1.5 hour, then at room temperature overnight. The volatiles were removed under reduced pressure and the residue was partitioned between dichloromethane (250 mL) and water (150 mL). The aqueous layer was extracted with dichloromethane (2 x 75 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford 18.9 g of *tert*-butyl 3-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propylcarbamate.

Part G

Concentrated hydrochloric acid (20 mL) was added to a suspension of *tert*-butyl 3-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propylcarbamate (12.55 g,

33.4 mmol) in methanol (135 mL). The resulting yellow solution was stirred for 48 hours and the liquid was removed via filtration. The resulting solid filter cake was dried overnight in a vacuum, oven at 40° C to afford 9.62 g of 3-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*]-1,5-naphthyridin-1-yl]propylamine hydrochloride as a pale yellow solid.

Part H

Triethylamine (4.0 mL, 28.8 mmol) was added to a suspension of 3-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*]-1,5-naphthyridin-1-yl]propylamine hydrochloride (3.0 g, 9.61 mmol) in dichloromethane (100 mL). Methanesulfonic anhydride (2.01 g, 11.53 mmol) was added to the reaction mixture and stirred for 1 hour at ambient temperature. The mixture was diluted with dichloromethane (50 mL) and saturated aqueous sodium bicarbonate and the layers were separated. The aqueous layer was extracted with dichlormethane (35 mL) and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated to afford 3.09 g of *N*-{3-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propyl}methanesulfonamide as a tan solid.

Part I

A reaction vessel was charged with acetone (100 mL) and cesium carbonate (3.13 g, 9.61 mmol). *N*-{3-[2-(Chloromethyl)-1*H*-imidazo[4,5-*c*]-1,5-naphthyridin-1-yl]propyl}methanesulfonamide (3.09 g, 8.73 mmol) was dissolved in acetone (40 mL) and methanol (10 mL) and added over 50 minutes to the reaction vessel. The reaction mixture was stirred at ambient temperature for 1 hour. The mixture was concentrated under reduced pressure and the residue was partitioned between water (75) mL and dichlormethane (100 mL). The layers were separated and the aqueous later was extracted with dichloromethane (40 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford 2.42 g of an orange solid. The material was triturated with acetonitrile to afford 1.75 g of 9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]-1,5-naphthyridine as a tan powder.

Part J

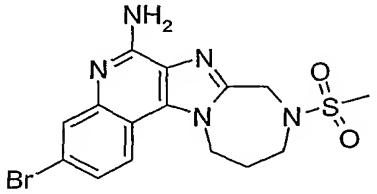
mCPBA (70% pure, 2.72 g, 11.03 mmol) was added to a solution of 9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]-1,5-naphthyridine (1.75 g, 5.51 mmol) in chloroform (30 mL) and stirred 2 hours at ambient temperature. Concentrated ammonium hydroxide (10 mL), chloroform (20 mL) and *p*-toluenesulfonyl chloride (1.16 g, 6.07 mmol) were sequentially added and the reaction mixture was stirred for 1 hour and then diluted with chloroform (20 mL) and additional *p*-toluenesulfonyl chloride (1.16 g, 6.07 mmol). The suspension was filtered and the resulting tan solid was triturated with 2M sodium hydroxide to afford 1.25 g of solid. The material was triturated with hot acetonitrile, hot methanol, and ethanol. The material was adsorbed onto 4 g of silica gel and purified by column chromatography on a HORIZON HPFC system (an automated, modular high-performance flash purification product available from Biotage, Inc, Charlottesville, Virginia, USA) (silica gel, eluting with 0-50% chloroform:methanol:ammonium hydroxide (CMA) in chloroform) and concentrated to afford a pale yellow solid. The material was triturated with hot methanol, filtered, and dried under high vacuum at 120 °C overnight to afford 9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]-1,5-naphthyridin-6-amine as beige needles, mp greater than 250 °C.

MS (ESI) *m/z* 333 $(M + H)^+$;

Anal. calcd for $C_{14}H_{16}N_6O_2S$: C, 50.59; H, 4.85; N, 25.28. Found: C, 50.30; H, 4.71; N, 25.19.

Example 365

3-Bromo-9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine



Part A

Triethylamine (8.9 mL, 64 mmol) and *tert*-butyl *N*-(3-aminopropyl)carbamate (30.95 g, 177.6 mmol) were added to a solution of 7-bromo-4-chloro-3-nitroquinoline

(42.55 g, 148.0 mmol, U.S. patent application publication no. US 2004/0147543, Example 1, Parts A through D) in DMF (500 mL), and the reaction was stirred for four days at ambient temperature. The reaction mixture was poured into water (2 L), and a precipitate formed. The precipitate was isolated by filtration and dried in a vacuum oven overnight at 65 °C to provide 56.4 g of *tert*-butyl 3-[(7-bromo-3-nitroquinolin-4-yl)amino]propylcarbamate.

Part B

A solution of *tert*-butyl 3-[(7-bromo-3-nitroquinolin-4-yl)amino]propylcarbamate (56.4 g, 133 mmol) in dichloromethane (150 mL) and ethyl acetate (500 mL) and 5% platinum on carbon (15.52 g, 79.56 mmol) were added to a hydrogenation vessel, which was placed under hydrogen pressure (50 psi, 3.4 x 10^5 Pa) and shaken overnight. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was dried under reduced pressure to provide 52.17 g of *tert*-butyl 3-[(3-amino-7-bromoquinolin-4-yl)amino]propylcarbamate.

Part C

Triethylamine (26.7 g, 264 mmol) was added to a solution of *tert*-butyl 3-[(3-amino-7-bromoquinolin-4-yl)amino]propylcarbamate (52.17 g, 132.0 mmol) in dichloromethane (370 mL). Chloroacetyl chloride (15.65 g, 138.6 mmol) was added, and the reaction was stirred overnight at ambient temperature. The solvent was removed under reduced pressure, and the residue was stirred in ethanol (1 L) overnight at ambient temperature. The solvent was removed under reduced pressure, and the residue was dissolved in chloroform. The resulting solution was washed twice with water, concentrated under reduced pressure, and dried under high vacuum to provide 41.63 g of *tert*-butyl 3-[7-bromo-2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propylcarbamate.

Part D

Potassium *tert*-butoxide (110 mL of a 1 M solution in THF) was added to a solution of *tert*-butyl 3-[7-bromo-2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propylcarbamate (41.63 g, 91.74 mmol) in THF (400 mL). The reaction was stirred for ten minutes at ambient temperature and concentrated under reduced pressure to provide

tert-butyl 3-bromo-11,12-dihydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(10*H*)-carboxylate in a crude mixture which was used without purification in Part E.

Part E

mCPBA (49.4 g of 77%, 220.2 mmol) was added to a solution of the material from Part D in chloroform (400 mL), and the reaction was stirred for 30 minutes at ambient temperature before additional mCPBA (about 1.3 equivalent) was added. The reaction mixture was stirred for two hours at ambient temperature. Ammonium hydroxide (350 mL) and *p*-toluenesulfonyl chloride (19.24 g, 100.9 mmol) were then added, and the reaction mixture was stirred vigorously overnight at ambient temperature. The organic layer was separated and concentrated under reduced pressure to provide *tert*-butyl 6-amino-3-bromo-11,12-dihydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(10*H*)-carboxylate in a crude mixture which was used without purification in Part F.

Part F

Hydrogen chloride (400 mL of a 4 N solution in 1,4-dioxane) was added to a solution of the material from Part E in methanol (350 mL). The reaction was stirred overnight at ambient temperature; a precipitate formed. Diethyl ether was added, and the precipitate was isolated by filtration, washed with diethyl ether, and dried under vacuum. The precipitate was then dissolved in hot methanol and treated with triethylamine to form the free base. The methanol and triethylamine were removed under reduced pressure, and the residue was washed several times with dichloromethane to provide 18.25 g of 3-bromo-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine.

Part G

Triethylamine (16.68 g, 164.8 mmol) and methanesulfonyl chloride (6.92 g, 60.4 mmol) were added to a solution of 3-bromo-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine (18.25 g, 54.94 mmol) in DMF (200 mL), and the mixture was stirred at ambient temperature overnight and filtered. After the solvent was removed under reduced pressure, the residue was suspended in acetonitrile to provide a solid, which was isolated by filtration to provide 1.87 g of 3-bromo-9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-

c]quinolin-6-amine. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluting with 2 N ammonia in methanol/chloroform in a 43-minute gradient from 0:100 to 15:85). In some fractions, the product crystallized and was isolated by filtration to provide 550.9 mg of product. The rest of the fractions containing the product were combined and concentrated under reduced pressure, and the residue was recrystallized from acetonitrile/ethanol to provide 1.426 g of 3-bromo-9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine as a light yellow solid, mp 303 °C.

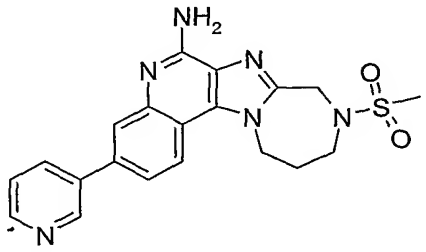
^{1}H NMR (300 MHz, DMSO-D6) δ 8.22 (d, J = 8.8 Hz, 1H), 7.74 (d, J = 2.1 Hz, 1H), 7.35 (dd, J = 8.8, 2.2 Hz, 1H), 6.85 (s, 2H), 4.86 (t, J = 4.5 Hz, 2H), 4.81 (s, 2H), 3.72 (t, J = 5.3 Hz, 2H), 2.80 (s, 3H), 2.24-2.16 (m, 2H); ^{13}C NMR (75 MHz, DMSO-D6) δ 153.1, 151.2, 146.9, 133.6, 128.3, 126.2, 123.7, 122.6, 120.0, 114.2, 49.6, 46.4, 45.7, 38.3, 27.7; MS (APCI) *m/z* 411 $(M + H)^+$;

Anal. Calcd for $C_{15}H_{16}BrN_5O_2S$: C, 43.91; H, 3.93; N, 17.07. Found: C, 44.07; H, 3.75; N, 17.32.

The mother liquor from the recrystallization was concentrated to provide an additional 5.43 g of product.

Example 366

9-(Methylsulfonyl)-3-pyridin-3-yl-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine



Sodium carbonate (0.140 g, 1.32 mmol), triphenylphosphine (74.7 mg, 0.33 mmol), 3-pyridine boronic acid (0.149 g, 1.21 mmol), and palladium (II) acetate (25 mg, 0.11 mmol) were sequentially added to a solution of 3-bromo-9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine (0.450 g, 1.1 mmol) in *n*-propanol (15 mL), methanol (10 mL), and water (5 mL). The reaction

was heated at 80 °C overnight and then concentrated under reduced pressure. The residue was mixed with dichloromethane, and the resulting solid was isolated by filtration. The solid was purified by column chromatography on silica gel (eluting with 2 N ammonia in methanol/chloroform in a gradient from 0% to 25%. The resulting solid was mixed with material from another run and purified again by column chromatography on silica gel under the same conditions to provide 76.8 mg of 9-(methylsulfonyl)-3-pyridin-3-yl-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine, as a beige solid, mp 302 °C.

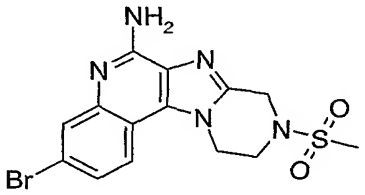
^{1}H NMR (300 MHz, DMSO-d6) δ 8.99 (d, J = 1.9 Hz, 1H), 8.60 (dd, J = 4.7, 1.4 Hz, 1H), 8.40 (d, J = 8.5 Hz, 1H), 8.18 (d, J = 6.2 Hz, 1H), 7.92 (s, 1H), 7.60 (dd, J = 8.6, 1.9 Hz, 1H), 7.54 (dd, J = 7.8, 4.9 Hz, 1H), 6.71 (s, 2H), 4.94 (t, J = 3.8 Hz, 2H), 4.84 (s, 2H), 3.74 (t, J = 4.9 Hz, 2H), 2.81 (s, 3H), 2.24-2.29 (m, 2H);

MS (APCI) *m/z* 409 $(M + H)^+$;

Anal. calcd for $C_{20}H_{20}N_6O_2S \cdot 0.3\ H_2O$: C, 58.04; H, 5.02; N, 20.31. Found: C, 58.18; H, 4.78; N, 20.25.

Example 367

3-Bromo-9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine



Part A

A modification of the method described in Part C of Example 365 was used to treat *tert*-butyl 2-[(3-amino-7-bromoquinolin-4-yl)amino]ethylcarbamate (66.69 g, 174.9 mmol, U.S. patent application publication no. US 2004/0147543, Example 386, Parts A and B) with triethylamine (35.4 g, 350 mmol) and chloroacetyl chloride (20.7 g, 183 mmol). After the reaction in ethanol was complete, a precipitate was present and was isolated by filtration to provide 38.42 g of *tert*-butyl 2-[7-bromo-2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethylcarbamate as white crystals. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel

(eluting with 2 N ammonia in methanol/chloroform in a 33-minute gradient from 0:100 to 5:95) to provide an additional 4.89 g of product.

Part B

The method described in Part D of Example 365 was used to treat *tert*-butyl 2-[7-bromo-2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethylcarbamate (10.0 g, 22.7 mmol) with potassium *tert*-butoxide (27.29 mL of a 1 M solution in THF) with the modification that the reaction was stirred overnight to provide *tert*-butyl 3-bromo-10,11-dihydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(8*H*)-carboxylate in a crude mixture.

Part C

A modification of the method described in Part E of Example 365 was used to treat the material from Part B with mCPBA followed by ammonium hydroxide (50 mL) and *p*-toluenesulfonyl chloride (4.76 g, 25.0 mmol). The mCPBA was added in three portions (1.2 equivalents, 0.2 equivalent, and 0.2 equivalent) over a period of 100 minutes. The product *tert*-butyl 6-amino-3-bromo-10,11-dihydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(8*H*)-carboxylate was obtained in a crude mixture.

Part D

Hydrogen chloride (50 mL of a 4 N solution in 1,4-dioxane) was added to a solution of the material from Part C in dichloromethane (50 mL) and methanol (10 mL). The reaction was stirred overnight at ambient temperature; a precipitate formed. Diethyl ether was added, and the precipitate was isolated by filtration and washed with dichloromethane and diethyl ether. The precipitate was then dissolved in hot methanol and treated with triethylamine (30 mL) to form the free base. The methanol and triethylamine were removed under reduced pressure, and the residue was diluted with dichloromethane. The resulting suspension was filtered to provide 6.47 g of 3-bromo-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine.

Part E

Triethylamine (3.82 g, 37.7 mmol) and methanesulfonyl chloride (2.38 g, 20.7 mmol) were sequentially added to a solution of 3-bromo-8,9,10,11-

tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine (6.00 g, 18.9 mmol) in DMF (50 mL), and the mixture was stirred at ambient temperature overnight. A precipitate formed and was isolated by filtration, washed with dichloromethane, and dried to provide 600 mg of 3-bromo-9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine as a white powder, mp 315 – 317 °C.

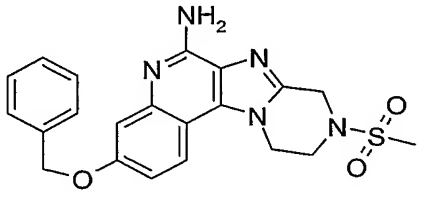
^{1}H NMR (300 MHz, DMSO-D6) δ 8.01 (d, J = 8.7 Hz, 1H), 7.75 (s, 1H), 7.39 (dd, J = 8.7, 1.9 Hz, 1H), 6.89 (s, 2H), 4.75-4.70 (m, 4H), 3.85 (t, J = 5.0 Hz, 2H), 3.13 (s, 3H); MS (APCI) *m/z* 397 $(M + H)^+$;

Anal. Calcd for $C_{14}H_{14}BrN_5O_2S$: C, 42.43; H, 3.56; N, 17.67. Found: C, 42.10; H, 3.45; N, 17.50.

The filtrate was concentrated under reduced pressure, and the solid residue was boiled in methanol, filtered, and washed with methanol, acetonitrile, dichloromethane, and diethyl ether to provide 906.7 mg of product. The filtrate was concentrated under reduced pressure, and the residue was triturated with dichloromethane and isolated by filtration to provide an additional 2.8 g of product as the hydrochloride salt.

Example 368

3-(Benzyloxy)-9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine



Part A

A mixture of triethyl orthoformate (92 mL, 0.55 mol) and 2,2-dimethyl-[1,3]-dioxane-4,6-dione (75.3 g, 0.522 mol) (Meldrum's acid) was heated at 55 °C for 90 minutes and then cooled to 45 °C. A solution of 3-benzyloxyaniline (100.2 g, 0.5029 mol) in methanol (200 mL) was slowly added to the reaction over a period 45 minutes while maintaining the reaction temperature below 50 °C. The reaction was then heated at 45 °C for one hour, allowed to cool to room temperature, and stirred overnight. The reaction mixture was cooled to 1 °C, and the product was isolated by filtration and washed with

cold ethanol (~400 mL) until the filtrate was colorless. 5-{[(3-Benzyloxy)phenylimino]methyl}-2,2-dimethyl-[1,3]-dioxane-4,6-dione (170.65 g) was isolated as a tan, powdery solid.

^{1}H NMR (300MHz, DMSO-d_6) : δ 11.21 (d, J = 14.2 Hz, 1H), 8.61 (d, J = 14.2 Hz, 1H), 7.49-7.30 (m, 7H), 7.12 (dd, J = 8.1, 1.96 Hz, 1H), 6.91 (dd, J = 8.4, 2.1 Hz, 1H), 5.16 (s, 2H), 1.68 (s, 6H).

Part B

A mixture of 5-{[(3-benzyloxy)phenylimino]methyl}-2,2-dimethyl-[1,3]-dioxane-4,6-dione (170.65 g, 0.483 mol) and DOWTHERM A heat transfer fluid (800 mL) was heated to 100 °C and then slowly added to a flask containing DOWTHERM A heat transfer fluid (1.3 L, heated at 210 °C) over a period of 40 minutes. During the addition, the reaction temperature was not allowed to fall below 207 °C. Following the addition, the reaction was stirred at 210 °C for one hour, and then allowed to cool to ambient temperature. A precipitate formed, which was isolated by filtration, washed with diethyl ether (1.7 L) and acetone (0.5 L), and dried in an oven to provide 76.5 g of 7-benzyloxyquinolin-4-ol as a tan powder.

^{1}H NMR (300MHz, DMSO-d_6) : δ 11.53 (s, 1H), 7.99 (dd, J = 2.4, 7.4Hz, 1H), 7.79 (d, J = 7.4Hz, 1H), 7.50-7.32 (m, 5H), 7.00 (s, 1H), 6.98 (dd, J = 2.5, 7.4Hz, 1H), 5.93 (d, J = 7.5Hz, 1H), 5.20 (s, 2H).

Part C

A mixture of 7-benzyloxyquinolin-4-ol (71.47 g, 0.2844 mol) and propionic acid (700 mL) was heated to 125 °C with vigorous stirring. Nitric acid (23.11 mL of 16 M) was slowly added over a period of 30 minutes while maintaining the reaction temperature between 121 °C and 125 °C. After the addition, the reaction was stirred at 125 °C for 1 hour then allowed to cool to ambient temperature. The resulting solid was isolated by filtration, washed with water, and dried in an oven for 1.5 days to provide 69.13 g of 7-benzyloxy-3-nitroquinolin-4-ol as a grayish powder.

^{1}H NMR (300MHz, DMSO-d_6) : δ 12.77 (s, 1H), 9.12 (s, 1H), 8.17 (dd, J = 3.3, 6.3Hz, 1H), 7.51-7.33 (m, 5H), 7.21-7.17 (m, 2H), 5.25 (s, 2H).

Part D

DMF (100 mL) was cooled to 0 °C, and phosphorous oxychloride (27.5 mL, 0.295 mol) was added dropwise. The resulting solution was stirred for 25 minutes and then added dropwise to a mixture of 7-benzyloxy-3-nitroquinolin-4-ol (72.87 g, 0.2459 mol) in DMF (400 mL). Following the addition, the reaction was heated at 100 °C for 5 minutes, cooled to ambient temperature, and poured into ice water with stirring. A tan precipitate formed, which was isolated by filtration and dissolved in dichloromethane. The resulting solution was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield 72.9 g of 7-benzyloxy-4-chloro-3-nitroquinoline as a light brown solid. ^{1}H NMR (300MHz, DMSO-d_6) : δ 9.34 (s, 1H), 8.36 (d, J = 8.7Hz, 1H), 7.71 (d, J = 2.4Hz, 1H), 7.66 (dd, J = 2.4, 9.3Hz, 1H), 7.56-7.51 (m, 2H), 7.46-7.34 (m, 3H), 5.40 (s, 2H).

Material from a separate run was used in the next step.

Part E

Triethylamine (58.9 mL, 422.4 mmol, 1.5 eq) and *tert*-butyl *N*-(2-aminoethyl) carbamate (54.1 g, 337.9 mmol, 1.2 eq) were added sequentially to a solution of 7-benzyloxy-4-chloro-3-nitroquinoline (88.63 g, 281.6 mmol) in DMF (800 mL) and stirred for 4 hours at ambient temperature. The crude reaction mixture was poured into hot water with continuous stirring to afford bright a yellow precipitate. The yellow solid was filtered and dried under reduced pressure at 65 °C to afford 123.65 g of *tert*-butyl 2-[(7-benzyloxy-3-nitroquinolin-4-yl)amino]ethylcarbamate.

Part F

tert-Butyl 2-[(7-benzyloxy-3-nitroquinolin-4-yl)amino]ethylcarbamate (40.0 g, 91.22 mmol) was dissolved in ethyl acetate (550 mL) and transferred to a Parr hydrogenation vessel charged with 5% platinum on carbon (10.68 g, 54.73 mmol, 0.03 eq). The vessel was purged with nitrogen gas and placed under hydrogen pressure (30 psi, 2.07 x 10^5 Pa) overnight. The catalyst was removed by filtration through a layer of CELITE filter aid, and the filter cake was rinsed with methanol and dichloromethane. The filtrate was concentrated under reduced pressure to provide 35.25 g *tert*-butyl 2-[(3-amino-7-benzyloxyquinolin-4-yl)amino]ethylcarbamate.

Part G

Triethylamine (24.0 mL, 172.58 mmol) was added to a solution of *tert*-butyl 2-[(3-amino-7-benzyloxyquinolin-4-yl)amino]ethylcarbamate (35.25 g, 86.29 mmol) in dichloromethane (400 mL), and the reaction was stirred at ambient temperature. Chloroacetyl chloride (6.87 mL, 86.29 mmol) was quickly added at ambient temperature, and the reaction was stirred for 10 minutes. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in ethanol (500 mL) and stirred for two days at ambient temperature. The mixture was concentrated under reduced pressure and the residue was recrystallized from dichloromethane to afford 6.23 g of *tert*-butyl 2-[7-benzyloxy-2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethylcarbamate. The mother liquor was divided into two portions which were separately purified by normal phase prep HPLC on silica gel (eluting with 2 N ammonia in methanol/chloroform in a 33-minute gradient from 0:100 to 5:95) and combined to provide an additional 24.21 g of product.

Part H

The method described in Part D of Example 365 was used to treat *tert*-butyl 2-[7-benzyloxy-2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethylcarbamate (23.55 g, 50.43 mmol) with potassium *tert*-butoxide (55.47 mL of a 1 M solution in THF) with the modification that crude product mixture was purified by normal phase prep HPLC on silica gel (eluting with 2 N ammonia in methanol/chloroform in a 66-minute gradient from 0:100 to 7:93) to provide 20.87 g of *tert*-butyl 3-benzyloxy-10,11-dihydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(8*H*)-carboxylate. Material from a different run was used in Part I.

Part I

mCPBA (0.782 g of 77% purity, 3.49 mmol) was added to a solution of *tert*-butyl 3-benzyloxy-10,11-dihydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(8*H*)-carboxylate (1.0 g, 2.3 mmol) in chloroform (15 mL), and the reaction was stirred for 30 minutes. Ammonium hydroxide (5 mL), and the reaction was stirred for five minutes before the rapid addition of *p*-toluenesulfonyl chloride (0.4865 g, 2.55 mmol). The reaction was stirred overnight at ambient temperature. The organic layer was separated and

concentrated under reduced pressure. The residue was purified by normal phase prep HPLC on silica gel (eluting with 2 N ammonia in methanol/chloroform in a 42-minute gradient from 0:100 to 5:95) to provide 550 mg of *tert*-butyl 6-amino-3-benzyloxy-10,11-dihydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(8*H*)-carboxylate.

Part J

Trifluoroacetic acid (10 mL of a 10% solution in dichloromethane) was added to *tert*-butyl 6-amino-3-benzyloxy-10,11-dihydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(8*H*)-carboxylate (0.550 g, 1.23 mmol), and the reaction was stirred at ambient temperature overnight. The solvent was removed under reduced pressure, and the residue was treated with hydrogen chloride (4 N in 1,4-dioxane). The solvent was removed under reduced pressure, and the residue was dissolved in methanol. Ammonia gas was bubbled through the resulting solution for 15 minutes, and then the solvent was removed under reduced pressure. The residue was dried overnight under vacuum to provide 3-benzyloxy-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine in a crude mixture, which was used in the next step without purification.

Part K

Triethylamine (498 mg, 4.92 mmol) and methanesulfonyl chloride (156 mg, 1.36 mmol) were sequentially added to a solution of the material from Part J in DMF (5 mL), and the mixture was stirred at ambient temperature overnight. The solvent was removed under reduced pressure, and the residue was purified by normal phase prep HPLC (eluting with 10% ammonium hydroxide in methanol/dichloromethane in a gradient from 0/100 to 10/90) followed by recrystallization from acetonitrile to provide 108 mg of 3-(benzyloxy)-9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine as a yellow powder, mp 266 - 268 °C.

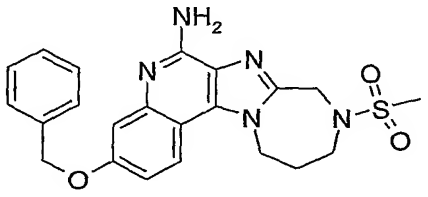
^{1}H NMR (300 MHz, DMSO-d6) δ 7.98 (d, J = 9.0 Hz, 1H), 7.51-7.33 (m, 5H), 7.14 (d, J = 2.6 Hz, 1H), 6.99 (dd, J = 8.9, 2.6 Hz, 1H), 6.54 (s, 2H), 5.21 (s, 2H), 4.72-4.68 (m, 4H), 3.84 (t, J = 5.4 Hz, 2H), 3.12 (s, 3H);

MS (APCI) *m/z* 424 $(M + H)^+$;

Anal. Calcd for $C_{21}H_{21}N_5O_3S$: C, 59.56; H, 5.00; N, 16.54. Found: C, 59.38; H, 4.88; N, 16.59.

Example 369

3-(Benzyloxy)-9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine



Part A

A modification of the method described in Part E of Example 367 was used to treat 7-benzyloxy-4-chloro-3-nitroquinoline (87.81 g, 279 mmol, Parts A through D of Example 367) with triethylamine (58.3 mL, 419 mmol) and *tert*-butyl *N*-(3-aminopropyl)carbamate (58.0 g, 334 mmol). The reaction was stirred overnight at ambient temperature. After filtration, the solid was washed with water and 1:1 cold 2-propanol:water. After the drying step 120.98 g of *tert*-butyl 3-[(7-benzyloxy-3-nitroquinolin-4-yl)amino]propylcarbamate were obtained.

Part B

tert-Butyl 3-[(7-benzyloxy-3-nitroquinolin-4-yl)amino]propylcarbamate (60.0 g, 132.6 mmol) was dissolved in ethyl acetate (400 mL) and transferred to a Parr hydrogenation vessel charged with 5% platinum on carbon (15.6 g, 80 mmol, 0.03 eq). The vessel was purged with nitrogen gas and placed under hydrogen pressure (50 psi, 3.45 x 10^5 Pa) overnight. The catalyst was removed by filtration through a layer of CELITE filter aid, and the filter cake was rinsed with methanol and dichloromethane. The filtrate was concentrated under reduced pressure to provide 52.4 g of *tert*-butyl 3-[(3-amino-7-benzyloxy-quinolin-4-yl)amino]propylcarbamate.

Part C

The method described in Part G of Example 368 was used to treat *tert*-butyl 3-[(3-amino-7-benzyloxy-quinolin-4-yl)amino]propylcarbamate (52.4 g, 124 mmol) with triethylamine (26.0 mL, 186 mmol) and chloroacetyl chloride (10.9 mL, 136.4 mmol). After recrystallization from dichloromethane 57.2 g of *tert*-butyl 3-[7-benzyloxy-2-

(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propylcarbamate (86% pure) were obtained.

Part D

Under a nitrogen atmosphere, potassium *tert*-butoxide (142.7 mL of a 1 M solution in THF) was added to a solution of *tert*-butyl 3-[7-benzyloxy-2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propylcarbamate (57.2 g, 118.9 mmol) in THF (142.7 mL). After the reaction was stirred at ambient temperature for ten minutes, additional potassium *tert*-butoxide (32 mL of a 1 M solution in THF) was added. The reaction was stirred overnight at ambient temperature and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (eluting with 2 N ammonia in methanol/chloroform in a 67-minute gradient from 0:100 to 3:97) and recrystallized sequentially from dichloromethane and acetonitrile to provide 26.99 g of *tert*-butyl 3-benzyloxy-11,12-dihydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(10*H*)-carboxylate.

Part E

Hydrogen chloride (25 mL of a 4 N solution in 1,4-dioxane) was added to a solution of *tert*-butyl 3-benzyloxy-11,12-dihydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(10*H*)-carboxylate in a 1:1 mixture of dichloromethane and diethyl ether (50 mL). The reaction was stirred overnight at ambient temperature; a precipitate formed. The precipitate was harvested via filtration and dried under reduce pressure to provide 9.66 g of 3-benzyloxy-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline.

Part F

Triethylamine (23.4 mL, 168 mmol) and methanesulfonyl chloride (2.18 mL, 28.0 mmol) were sequentially added to a solution of the material from Part E in DMF (75 mL), and the mixture was stirred for three hours. Additional methanesulfonyl chloride (2.18 mL) was added and the mixture was stirred for one hour. The addition of sodium carbonate and heating did not increase the rate of conversion. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on a

COMBIFLASH system (eluting with 2 N ammonia in methanol/chloroform in a 33-minute gradient from 0:100 to 10:90) followed by recrystallization (3 x) from isopropanol to provide 4.65 g of 3-(benzyloxy)-9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline.

Part G

mCPBA (2.96 g of 77% purity, 13.2 mmol) was added to a solution of 3-(benzyloxy)-9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline (4.648 g, 11 mmol) in chloroform (20 mL), and the reaction was stirred for 10 minutes. Additional mCPBA (1.5 g) was added and the reaction was monitored for disappearance of the starting substrate by thin-layer chromatography (TLC). Ammonium hydroxide (20 mL) was then added and the reaction was stirred for five minutes before the rapid addition of *p*-toluenesulfonyl chloride (2.31 g, 12.1 mmol). The reaction was stirred overnight at ambient temperature. The organic layer was separated, washed with ammonium hydroxide, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluting with 2 N ammonia in methanol/chloroform in a 43-minute gradient from 1:99 to 25:75) and recrystallization from isopropanol and dried in a vacuum oven at 65 °C to afford 1.1 g of 3-(benzyloxy)-9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine as brown crystals, mp 235 – 236°C.

^{1}H NMR (300 MHz, DMSO-d6) δ 8.17 (d, J = 9.1 Hz, 1H), 7.50-7.32 (m, 5H), 7.13 (d, J = 2.7 Hz, 1H), 6.95 (dd, J = 9.0, 2.7 Hz, 1H), 6.55 (s, 2H), 5.21 (s, 2H), 4.84 (t, J = 3.8 Hz, 2H), 4.79 (s, 2H), 3.71 (t, J = 5.0 Hz, 2H), 2.78 (s, 3H), 2.22-2.14 (m, 2H);

^{13}C NMR (75 MHz, DMSO-D6) δ 157.6, 152.6, 150.0, 147.5, 137.6, 134.2, 128.8, 128.1, 127.9, 124.7, 121.7, 112.0, 109.5, 109.1, 69.4, 49.7, 46.1, 45.7, 38.3, 27.8;

MS (APCI) *m/z* 438 $(M + H)^+$;

Anal. Calcd for $C_{22}H_{23}N_5O_3S$: C, 60.40; H, 5.30; N, 16.01. Found: C, 60.39; H, 5.39; N, 15.98.

An additional 6.37 g of solid of 76% purity was isolated by filtration during the recrystallization and used in Examples 489 - 492.

Examples 370-385

A solution of 3-bromo-9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine (41 mg, 0.10 mmol, Example 365) in 7:3 (v/v) chloroform/methanol (2 mL) was added to a test tube. The solvent was removed by vacuum centrifugation. A boronic acid or ester selected from the table below (0.11 mmol) was added followed by *n*-pronanol (1.6 mL), palladium (II) acetate (0.150 mL of a 4 mg/mL solution in toluene, 0.0026 mmol), aqueous sodium carbonate (0.600 mL of 2 M, 1.2 mmol), water (0.113 mL), and triphenylphosphine (0.053 mL of a 15 mol% solution in n-propanol, 0.0078 mmol). The tube was purged with nitrogen and then heated at 80 °C overnight. Methanol (1 mL) was added followed by palladium (II) acetate, aqueous sodium carbonate, and triphenylphosphine in the amounts listed above. The tube was purged with nitrogen and then heated at 80 °C overnight.

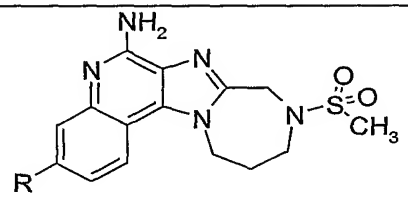
For example 373, the solvent was removed by vacuum centrifugation. Glacial acetic acid (3 mL), THF (1 mL), and deionized water (1 mL), and the reaction was heated at 60 °C overnight. 3-Bromo-5-(*tert*-butyldimethylsilanyloxymethyl)pyridine was prepared according to the published procedure (Zhang, N. et al, *J. Med. Chem.*, *45*, 2832-2840 (2002)). Under a nitrogen atmosphere, a solution of 3-bromo-5-(*tert*-butyldimethylsilanyloxymethyl)pyridine (28.70 g, 94.94 mmol) and triisopropyl borate (26.3 mL, 114 mmol) in dry THF was cooled to -70 °C. *n*-Butyllithium (45.6 mL, 114 mmol) was added dropwise over a period of 1.5 hours. The reaction was stirred for an additional 30 minutes and then allowed to warm to -20 °C. Dilute aqueous ammonium chloride was added, and the mixture was allowed to warm to ambient temperature. The aqueous layer was separated and extracted with diethyl ether. The combined organic fractions were concentrated under reduced pressure, and methanol was added to the resulting oil. A solid formed, which was stirred with water for two days, isolated by filtration, and dried under reduced pressure to provide 18.19 g of 5-(*tert*-butyldimethylsilanyloxymethyl)pyridine-3-boronic acid as a white solid.

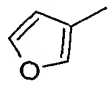
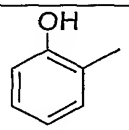
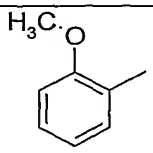
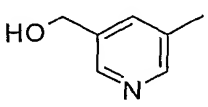
For each of Examples 370 through 385, the product from the coupling reaction was dissolved in 1N hydrochloric acid (3 mL) to adjust to pH 5-7 and passed through a Waters OASIS Sample Extractions Cartridge MCX (6 cc) optionally using light nitrogen pressure. The cartridge was washed with methanol (5 mL) optionally using light nitrogen pressure and transferred to a clean test tube. A solution of 1% ammonia in methanol (2 x 5 mL)

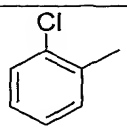
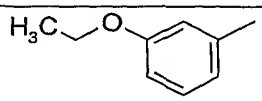
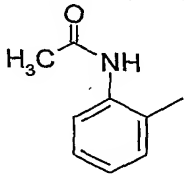
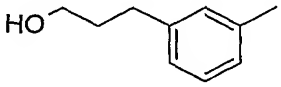
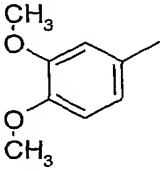
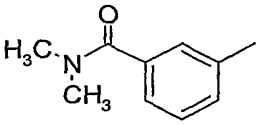
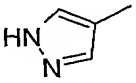
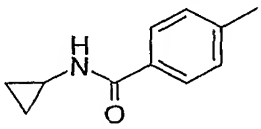
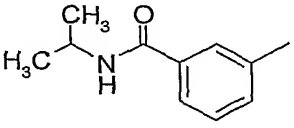
was then passed through the cartridge optionally using light nitrogen pressure, and the basic solution was collected and concentrated.

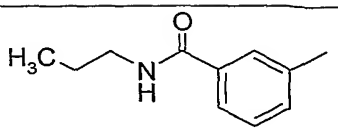
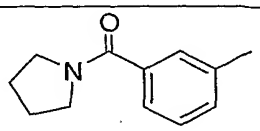
Each compound was purified by prep HPLC using a Waters FractionLynx automated purification system. The prep HPLC fractions were analyzed using a Waters LC/TOF-MS, and the appropriate fractions were centrifuge evaporated to provide the trifluoroacetate salt of the desired compound. Reversed phase preparative liquid chromatography was performed with non-linear gradient elution from 5-95% B where A is 0.05% trifluoroacetic acid/water and B is 0.05% trifluoroacetic acid/acetonitrile. Fractions were collected by mass-selective triggering. The table below shows the boronic acid or ester used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

Examples 370-385



Example	Reagent	R	Measured Mass (M+H)
370	Furan-3-boronic acid		398.1264
371	(2-Hydroxyphenyl)boronic acid		424.1456
372	2-Methoxyphenylboronic acid		438.1566
373	5-(*tert*-Butyldimethylsilanyloxymethyl)pyridine-3-boronic acid		439.1526

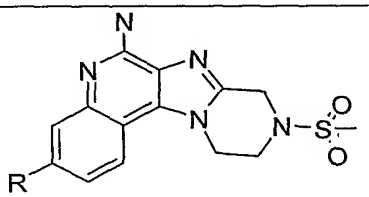
374	2-Chlorophenylboronic acid		442.1070
375	4-(*N*,*N*-Dimethylamino)phenylboronic acid		451.1943
376	3-Ethoxyphenylboronic acid		452.1750
377	(2-Acetylaminophenyl)boronic acid		465.1722
378	[3-(Hydroxypropyl)phenyl]boronic acid		466.1880
379	3,4-Dimethoxyphenylboronic acid		468.1718
380	3-(*N*,*N*-Dimethylaminocarbonyl)phenylboronic acid		479.1856
381	4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole		398.1390
382	4-(Cyclopropylaminocarbonyl)phenylboronic acid		491.1838
383	3-(*N*-Isopropylaminocarbonyl)phenylboronic acid		493.2057

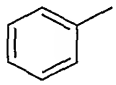
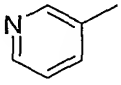
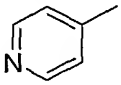
384	3-(*N*-Propylaminocarbonyl)phenylboronic acid		493.1985
385	3-(Pyrrolidine-1-carbonyl)phenylboronic acid		505.1983

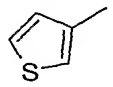
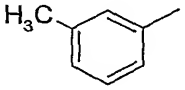
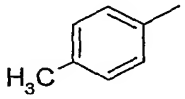
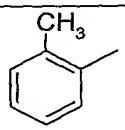
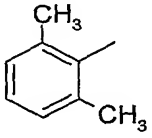
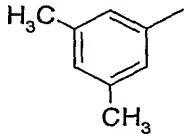
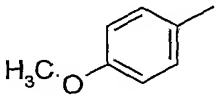
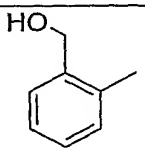
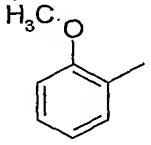
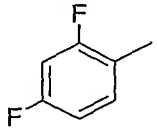
Examples 386-398

A modification of the method described in Examples 371-386 was followed using 3-bromo-9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine (39 mg, 0.1 mmol, Example 367) in lieu of 3-bromo-9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine. The reactions were heated overnight only once. Each compound was purified on a Waters OASIS Sample Extractions Cartridge MCX followed by prep HPLC as described in Examples 370-385. The table below shows the boronic acid or ester used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

Examples 386-398



Example	Reagent	R	Measured Mass (M+H)
386	Phenylboronic acid		394.1363
387	Pyridine-3-boronic acid		395.1311
388	Pyridine-4-boronic acid		395.1287

389	Thiophene-3-boronic acid		400.0939
390	3-Methylphenylboronic acid		408.1512
391	4-Methylphenylboronic acid		408.1523
392	*o*-Tolylboronic acid		408.1462
393	2,6-Dimethylphenylboronic acid		422.1665
394	3,5-Dimethylphenylboronic acid		422.1659
395	4-Methoxyphenylboronic acid		424.1437
396	(2-Hydroxymethylphenyl)boronic acid dehydrate		424.1472
397	2-Methoxyphenylboronic acid		424.1464
398	2,4-Difluorophenylboronic acid		430.1167

Examples 399-424

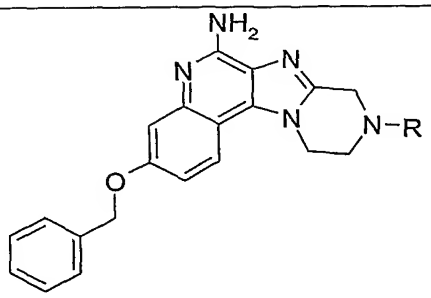
Hydrogen chloride (20 mL of a 4 N solution in 1,4-dioxane) and methanol (20 mL) were added to *tert*-butyl 6-amino-3-benzyloxy-10,11-

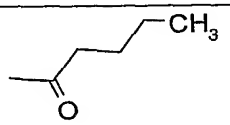
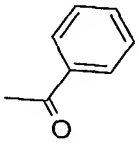
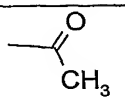
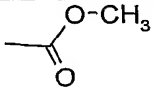
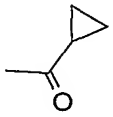
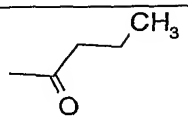
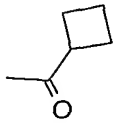
dihydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(8*H*)-carboxylate (4.45 g, 9.98 mmol, prepared by the methods described in Example 368 Parts A through I), and the reaction was stirred at ambient temperature overnight. A precipitate was present and was isolated by filtration and washed with cold methanol. The solid was then recrystallized from methanol, isolated by filtration, washed with diethyl ether, and dried overnight under vacuum at 65 °C to provide 3.89 g of 3-benzyloxy-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine hydrochloride as a white solid.

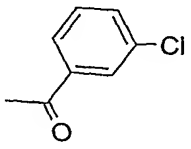
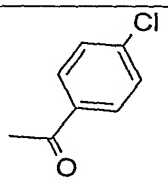
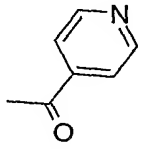
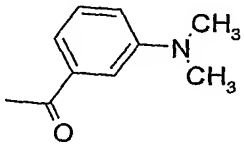
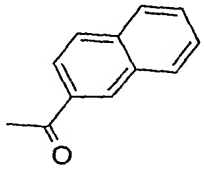
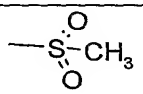
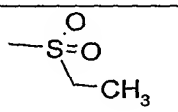
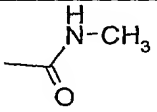
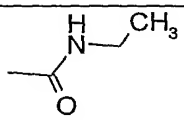
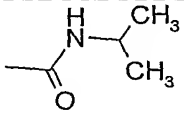
Part B

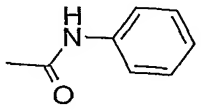
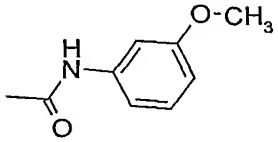
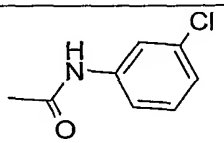
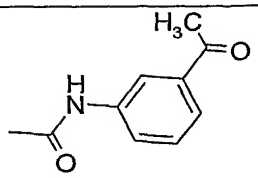
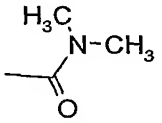
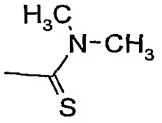
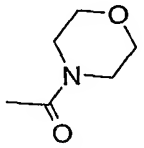
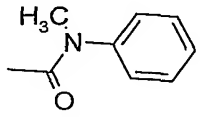
A reagent (0.11 mmol) indicated in the table below was added to a solution of 8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine hydrochloride (38 mg, 0.0995 mmol) and triethylamine (0.070 mL, 0.50 mmol) in pyridine (1 mL) in a test tube. The test tube was capped and shaken overnight at ambient temperature. Two drops of deionized water were added to each test tube, and the solvent was removed by vacuum centrifugation. The compounds were purified by prep HPLC according to the method described in Examples 370-385. The table below shows the acid chloride, sulfonyl chloride, isocyanate, or carbamoyl chloride used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

Examples 399 - 424



Example	Reagent	R	Measured Mass (M+H)
399	None	—H	346.1659
400	Pentanoyl chloride		430.2242
401	Benzoyl chloride		450.1914
402	Acetyl chloride		388.1769
403	Methyl chloroformate		404.1718
404	Cyclopropanecarbonyl chloride		414.1932
405	Butyryl chloride		416.2075
406	Cyclobutanecarbonyl chloride		428.2071

407	3-Chlorobenzoyl chloride		484.1529
408	4-Chlorobenzoyl chloride		484.1533
409	Isonicotinoyl chloride hydrochloride		451.1872
410	3-Dimethylaminobenzoyl chloride		493.2340
411	2-Naphthoyl chloride		500.2072
412	Methanesulfonyl chloride		424.1447
413	Ethanesulfonyl chloride		438.1605
414	Methyl isocyanate		403.1895
415	Ethyl isocyanate		417.2047
416	Isopropyl isocyanate		431.2183

417	Phenyl isocyanate		465.2010
418	3-Methoxyphenyl isocyanate		495.2148
419	3-Chlorophenyl isocyanate		499.1616
420	3-Acetylphenyl isocyanate		507.2122
421	*N,N*-Dimethylcarbamoyl chloride		417.2033
422	*N,N*-Dimethylthiocarbamoyl chloride		433.1782
423	4-Morpholinylcarbonyl chloride		459.2137
424	*N*-Methyl-*N*-Phenylcarbamoyl chloride		479.2176

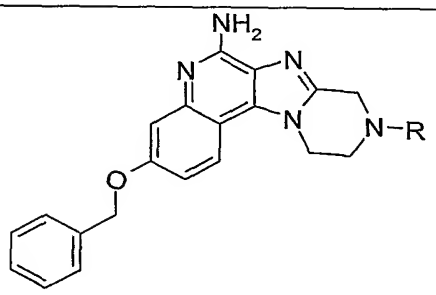
Examples 425 - 434

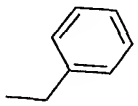
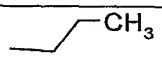
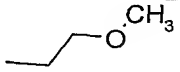
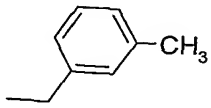
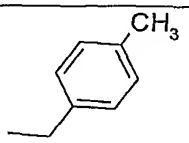
Potassium carbonate (55 mg, 0.40 mmol) was added to a test tube. A solution of 8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine hydrochloride (35 mg, 0.091 mmol) in anhydrous DMF (1 mL) was then added to the tube followed by an alkylating agent (0.11 mmol) from the table below. The tube was capped, shaken overnight at ambient temperature, and filtered. The filtrate was concentrated under

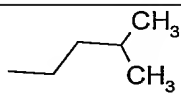
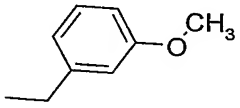
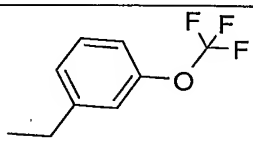
reduced pressure, and the residue was purified by prep HPLC according to the method described in Examples 370-385. The table below shows the alkylating agent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

5

Examples 425 - 434



Example	Reagent	R	Measured Mass (M+H)
	None	—H	346.1648
425	Benzyl bromide		436.2146
426	1-Bromopropane		388.2144
427	(Bromomethyl)cyclopropane		400.2142
428	2-Bromoethyl methyl ether		404.2107
429	Iodomethane	—CH_3	360.1815
430	*alpha*-Bromo-*m*-xylene		450.2265
431	*alpha*-Bromo-*p*-xylene		450.2272

432	1-Iodo-3-methylbutane		416.2420
433	3-Methoxybenzyl bromide		466.2237
434	3-(Trifluoromethoxy)benzyl bromide		520.1960

Examples 435 - 450

Part A

The methods described in Part I of Example 368 were used to treat *tert*-butyl 3-benzyloxy-11,12-dihydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(10*H*)-carboxylate (5.52 g, 12.4 mmol, Example 369 Parts A through D) with mCPBA (4.17 g of 77% purity, 18.6 mmol) followed by ammonium hydroxide (25 mL) and *p*-toluenesulfonyl chloride (2.6 g, 13.7 mmol) and purify the final compound to provide 2.07 g of *tert*-butyl 6-amino-3-benzyloxy-11,12-dihydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(10*H*)-carboxylate.

Part B

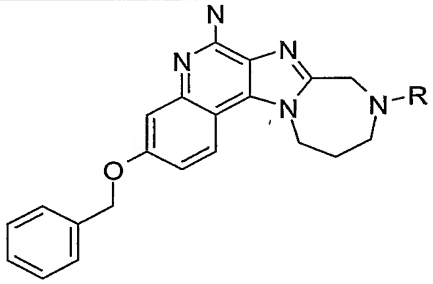
Trifluoroacetic acid (50 mL of a 10% solution in dichloromethane) was added to *tert*-butyl 6-amino-3-benzyloxy-11,12-dihydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(10*H*)-carboxylate (2.07 g, 4.50 mmol), and the reaction was stirred at ambient temperature overnight. The solvent was removed under reduced pressure, and the residue was recrystallized from methanol to provide 2.2 g of 3-benzyloxy-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine trifluoroacetate.

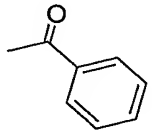
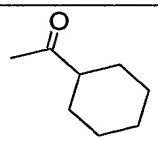
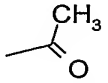
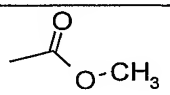
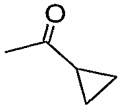
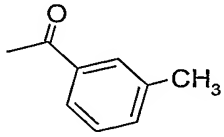
Part C

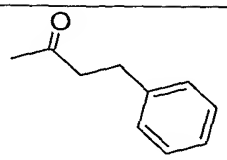
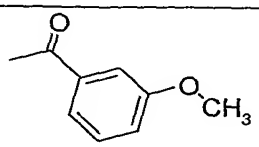
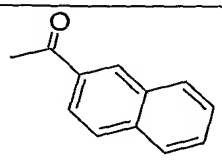
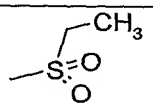
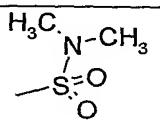
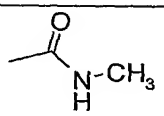
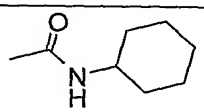
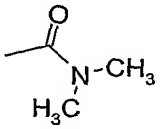
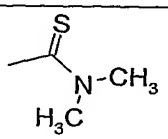
A reagent (0.12 mmol) indicated in the table below was added to a solution of 3-benzyloxy-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine trifluoroacetate (36 mg, 0.10 mmol) and *N,N*-diisopropylethylamine (0.070 mL, 0.40 mmol) in anhydrous DMF (1 mL) in a test tube. The test tube was capped and

shaken overnight. The solvent was removed by vacuum centrifugation. The compound was purified by prep HPLC using the method described in Examples 370-385. The table below shows the acid chloride, sulfonyl chloride, isocyanate, or carbamoyl chloride used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

Examples 435-450



Example	Reagent	R	Measured Mass (M+H)
435	None	—H	360.1842
436	Benzoyl chloride		464.2120
437	Cyclohexanecarbonyl chloride		470.2586
438	Acetyl chloride		402.1971
439	Methyl chloroformate		418.1903
440	Cyclopropanecarbonyl chloride		428.2110
441	*m*-Toluoyl chloride		478.2238

442	Hydrocinnamoyl chloride		492.2409
443	3-Methoxybenzoyl chloride		494.2221
444	2-Naphthoyl chloride		514.2272
445	Ethanesulfonyl chloride		452.1761
446	Dimethylsulfamoyl chloride		467.1874
447	Methyl isocyanate		417.2078
448	Cyclohexyl isocyanate		485.2679
449	*N,N*-Dimethylcarbamoyl chloride		431.2229
450	*N,N*-Dimethylthiocarbamoyl chloride		447.1956

Examples 451 - 467

Part A

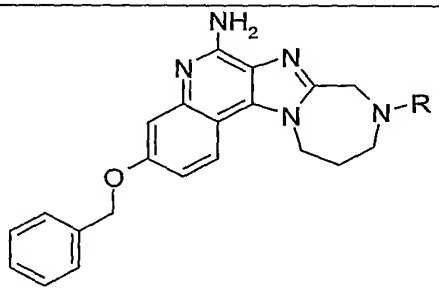
Hydrogen chloride (20 mL of 4 N in 1,4-dioxane) was added to a solution of *tert*-butyl 6-amino-3-benzyloxy-11,12-dihydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(10*H*)-carboxylate (3.89 g, 8.46 mmol, prepared as described in Part A of

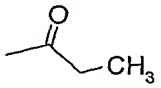
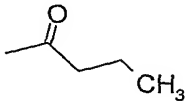
Examples 435-450) in dichloromethane (50 mL), and the reaction was stirred at ambient temperature for one hour. Diethyl ether was added, and a precipitate formed. The precipitate was isolated by filtration and dried in a vacuum oven at 65 °C to provide 3.52 g of 3-benzyloxy-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine dihydrochloride.

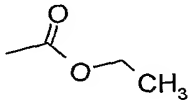
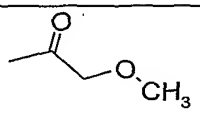
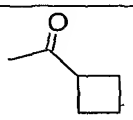
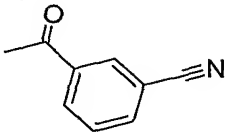
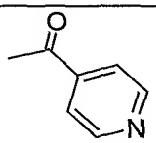
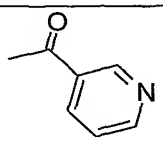
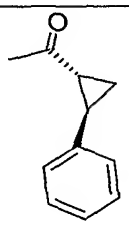
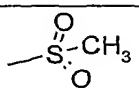
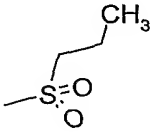
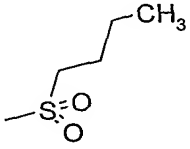
Part B

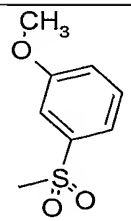
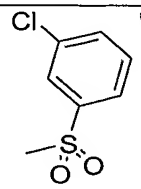
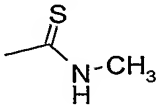
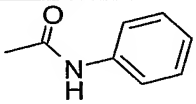
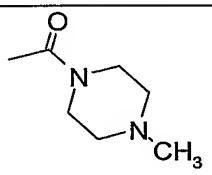
A reagent (0.11 mmol) indicated in the table below was added to a solution of 3-benzyloxy-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine dihydrochloride (42 mg, 0.098 mmol) and *N,N*-diisopropylethylamine (0.070 mL, 0.40 mmol) in anhydrous DMF (1 mL) in a test tube. The test tube was capped and shaken overnight. Two drops of water were added, and the solvent was removed by vacuum centrifugation. The compound was purified by prep HPLC using the method described in Examples 370-385. The table below shows the acid chloride, sulfonyl chloride, isocyanate, or carbamoyl chloride used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

Examples 451 – 467



Example	Reagent	R	Measured Mass (M+H)
	None	—H	360.1861
451	Propionyl chloride		416.2085
452	Butyryl chloride		430.2271

453	Ethyl chloroformate		432.2064
454	Methoxyacetyl chloride		432.2014
455	Cyclobutanecarbonyl chloride		442.2214
456	3-Cyanobenzoyl chloride		489.2009
457	Isonicotinoyl chloride hydrochloride		465.2044
458	Nicotinoyl chloride hydrochloride		465.2051
459	*trans*-2-Phenyl-1-cyclopropanecarbonyl chloride		504.2393
460	Methanesulfonyl chloride		438.1577
461	1-Propanesulfonyl chloride		466.1910
462	1-Butanesulfonyl chloride		480.2042

463	3-Methoxybenzenesulfonyl chloride		530.1879
464	3-Chlorobenzenesulfonyl chloride		534.1348
465	Methyl isothiocyanate		433.1771
466	Phenyl isocyanate		479.2170
467	4-Methyl-1-piperazinecarbonyl chloride		486.2587

Examples 468 - 480

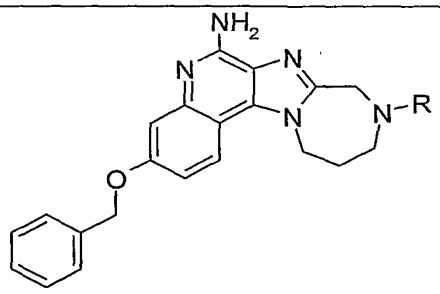
An aldehyde or ketone (0.12 – 0.13 mmol) indicated in the table below was added to a solution of 3-benzyloxy-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine trifluoroacetate (35.6 mg, 0.0931 mmol) in anhydrous DMF (1 mL) in a test tube. The test tube was capped and shaken for 30 minutes. Borane-pyridine complex (13 μL, 0.104 mmol) was added, and the reaction was shaken overnight.

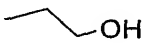
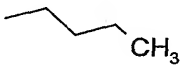
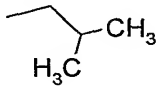
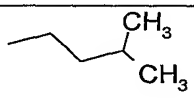
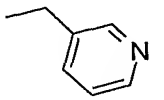
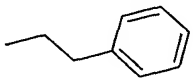
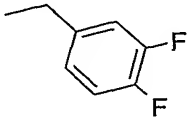
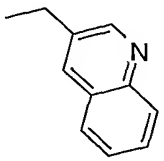
For examples 476-480, additional ketone (0.12 – 0.13 mmol) was added, and the reaction was shaken for 10 minutes. Additional borane-pyridine complex (13 μL, 0.104 mmol) was added, and the reaction was shaken for six hours.

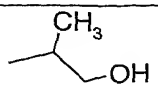
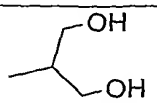
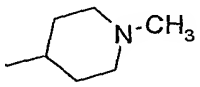
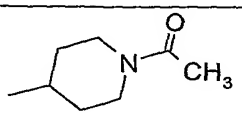
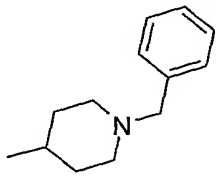
For each reaction, the solvent was removed by vacuum centrifugation. The compounds were purified by prep HPLC according to the method described in Examples 370-385. The table below shows aldehyde or ketone used for each example, the structure

of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

Example 468 - 480



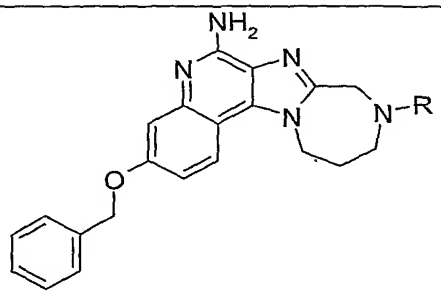
Example	Reagent	R	Measured Mass (M+H)
	None	—H	360.1839
468	2-Hydroxyacetaldehyde		404.2066
469	Butyraldehyde		416.2430
470	Isobutyraldehyde		416.2477
471	Isovaleradehyde		430.2608
472	Nicotinaldehyde		451.2253
473	Phenylacetaldehyde		464.2458
474	3,4-Difluorobenzaldehyde		486.2124
475	Quinoline-3-carboxaldehyde		501.2393

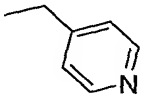
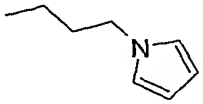
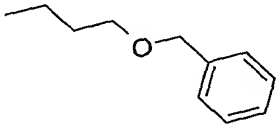
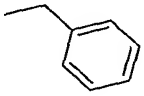
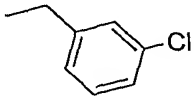
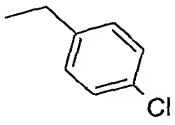
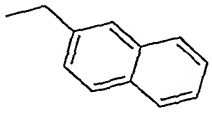
476	Hydroxyacetone		418.2253
477	Dihydroxyacetone		434.2203
478	1-Methyl-4-piperidone		457.2745
479	1-Acetyl-4- piperidone		485.2658
480	1-Benzyl-4-piperidone		533.3030

Examples 481 - 488

The methods described in Examples 425-434 were used to treat 3-benzyloxy-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine dihydrochloride (43 mg, 0.10 mmol) with potassium carbonate (55 mg, 0.40 mmol) and an alkylating agent (0.11 mmol) from the table below and purify the final compound. The table below shows the alkylating agent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

Examples 481 - 488



Example	Reagent	R	Measured Mass (M+H)
481	(Bromomethyl)cyclopropane		414.2291
482	4-(Bromomethyl)pyridine hydrobromide		451.2216
483	1-(3-Bromopropyl)pyrrole		467.2535
484	Benzyl 3-bromopropyl ether		508.2660
485	Benzyl bromide		450.2270
486	3-Chlorobenzyl bromide		484.1869
487	4-Chlorobenzyl bromide		484.1877
488	2-(Bromomethyl)naphthalene		500.2404

Examples 489 - 492

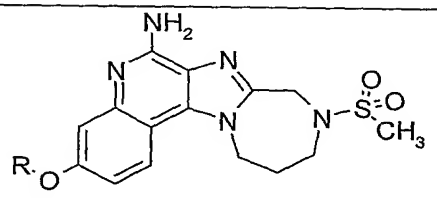
Part A

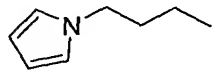
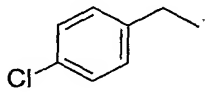
3-(Benzyloxy)-9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine, (6.37 g, 14.56 mmol) prepared as described in Example 369, was dissolved in methanol (150 mL) and transferred to a hydrogenation vessel charged with 10% palladium on carbon (12.4 g, 116 mmol). The vessel was purged with nitrogen gas and placed under hydrogen pressure (50 psi, 3.45 x 10^5 Pa) and shaken for 3 days at ambient temperature. The catalyst was removed by filtration. The filtrate was concentrated under reduced pressure, and the residue crystallized from isopropanol. The material was purified by column chromatography on silica gel (eluting with 2 N ammonia in methanol/chloroform in a 47-minute gradient from 5:95 to 50:50) and crystallized from isopropanol to provide 1.15 g of 6-amino-9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-3-ol.

Part B

Potassium carbonate (55 mg, 0.40 mmol) was added to a test tube. A solution of 6-amino-9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-3-ol (36 mg, 0.10 mmol) in anhydrous *N,N*-dimethylacetamide (DMA) (1 mL) was then added to the tube followed by an alkylating agent (0.15 mmol) from the table below. The tube was capped, shaken overnight at ambient temperature, heated at 50 °C over a second night, and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by prep HPLC according to the method described in Examples 370-385. The table below shows the alkylating agent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

Examples 489 - 492



Example	Reagent	R	Measured Mass (M+H)
489	None	H	348.1132
490	Iodomethane	H_3C	362.1277
491	1-(3-Bromopropyl)pyrrole		455.1890
492	4-Chlorobenzyl bromide		472.1219

Examples 493 - 494

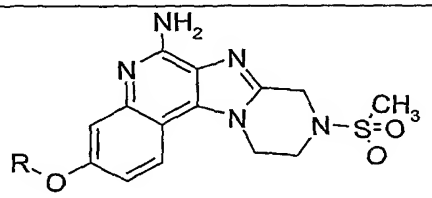
Part A

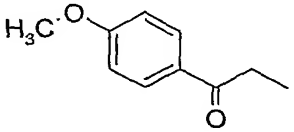
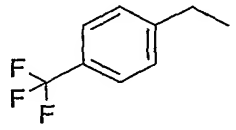
3-(Benzyloxy)-9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine, (3.34 g, 10.0 mmol) prepared as described in Example 368, was dissolved in a mixture of methanol (100 mL) and dichloromethane (100 mL) and transferred to a hydrogenation vessel charged with 10% palladium on carbon (5 g, 47 mmol). The vessel was placed under hydrogen pressure (50 psi, 3.45 x 10^5 Pa) and shaken for two days at ambient temperature. An analysis by LC/MS indicated the presence of starting material. The catalyst was removed by filtration through a layer of CELITE filter aid, and the filtrate was placed under hydrogen pressure (50 psi, 3.45 x 10^5 Pa) again for two days in the presence of 10% palladium on carbon (5 g, 47 mmol). The catalyst was removed by filtration through a layer of CELITE filter aid, and the filtrate was concentrated under reduced pressure. The residue (560 mg) was combined with material from another run to provide 1.19 g of 6-amino-9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-3-ol.

Part B

A modification of the method described in Examples 489 - 492 was used to treat 6-amino-9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-3-ol (33 mg, 0.10 mmol) with potassium carbonate (55 mg, 0.40 mmol) and an alkylating agent (0.13 mmol) from the table below. DMF was used as in lieu of DMA, and heating at 50 °C was carried out for four hours. Each product was purified by prep HPLC according to the method described in Examples 370-385. The table below shows the alkylating agent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

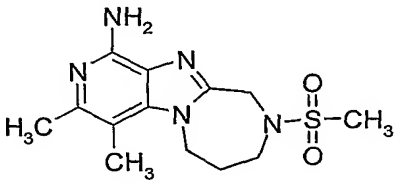
Examples 493 - 494



Example	Reagent	R	Measured Mass (M+H)
493	2-Bromo-4'-Methoxyacetophenone		482.1505
494	4-(Trifluoromethyl)benzyl Bromide		492.1306

Example 495

3,4-Dimethyl-9-(methylsulfonyl)-7,8,9,10-tetrahydro-6*H*-pyrido[3',4':4,5]imidazo[1,2-*a*][1,4]diazepin-1-amine



Part A

tert-Butyl 3-[(3-amino-5,6-dimethyl-2-phenoxypyridin-4-yl)amino]propylcarbamate (68.8 g, 178 mmol), prepared as described in U.S. Patent No. 6,545,016, Example 17, Parts A through C, was dissolved in chloroform (600 mL). Ethyl 2-chloroacetimidate hydrochloride (56.0 g, 354 mmol) was added to the solution and the reaction mixture was stirred at 60 °C for 72 hours. The reaction mixture was diluted with chloroform (200 mL), washed with brine (2 x 600 mL), and the layers were separated. The combined organics were dried over magnesium sulfate, filtered through CELITE filter aid, and concentrated under reduced pressure to afford 91.62 g of *tert*-butyl 3-[2-(chloromethyl)-6,7-dimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl]propylcarbamate.

Part B

tert-Butyl 3-[2-(chloromethyl)-6,7-dimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl]propylcarbamate (90.0 g, 202 mmol) was dissolved in THF (800 mL) and dichloromethane (800 mL) and cooled to 0 °C. Potassium *tert*-butoxide (30.0 mL of a 1 M solution in THF) was added and the reaction mixture was stirred overnight at ambient temperature and at 60 °C for two hours. Additional potassium *tert*-butoxide solution (30.0 mL) was added to the reaction mixture and heated at 60 °C for three hours. Additional potassium *tert*-butoxide solution (30.0 mL) was added to the reaction mixture and heated at 60 °C overnight. Addition of 250 mL of potassium *tert*-butoxide solution to the reaction mixture followed. The reaction mixture was stirred for 2.5 hours and the reaction mixture was concentrated under reduced pressure. The residue was dissolved in 800 mL of ethyl acetate and washed with brine (5 x 500 mL). The combined organic layers were dried over magnesium sulfate, filtered through CELITE filter aid, and concentrated under reduced pressure to afford 75.0 g of a dark brown solid. A portion of the material (44.0 g)

was subjected to column chromatography on silica gel (eluting with a gradient of 1:2000 methanol in dichloromethane to 2:1:97 methanol:ammonium hydroxide:dichloromethane). The resulting material was further subjected to column chromatography on silica gel (eluting with 0.5-1:1:97.5-98 methanol:ammonium hydroxide:dichloromethane) four additional times and concentrated under reduced pressure to afford 28.92 g of *tert*-butyl 3,4-dimethyl-1-phenoxy-7,8-dihydro-6*H*-pyrido[3',4':4,5]imidazo[1,2-*a*][1,4]diazepine-9(10*H*)-carboxylate as a light brown solid.

Part C

Ammonia (260 mL of a 7 N solution in methanol) and *tert*-butyl 3,4-dimethyl-1-phenoxy-7,8-dihydro-6*H*-pyrido[3',4':4,5]imidazo[1,2-*a*][1,4]diazepine-9(10*H*)-carboxylate (8.61 g, 21.0 mmol) were placed in a sealed glass container and heated to 170 °C overnight. The reaction mixture was cooled to ambient temperature and dissolved in ethanol (100 mL). Hydrochloric acid (45 mL, 12 M) was added to the reaction mixture and stirred at 90 °C and stirred overnight. The mixture was cooled to ambient temperature and concentrated under reduced pressure to afford 8.01 g of a dark brown material. The material was rinsed with diethyl ether and dissolved with methanol. The mixture was treated with hydrogen chloride (a 4 N solution in 1,4-dioxane) and concentrated under reduced pressure. The resulting material was slurried with diethyl ether and filtered. The filter cake was washed with diethyl ether, and the resulting solid was dried under reduced pressure. The material was slurried with hot acetonitrile and filtered to afford 6.55 g of 3,4-dimethyl-7,8,9,10-tetrahydro-6*H*-pyrido[3',4':4,5]imidazo[1,2-*a*][1,4]diazepin-1-amine dihydrochloride. Material from a separate run was used in the next step.

Part D

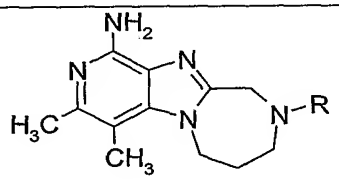
Methanesulfonyl chloride (198 mg, 1.73 mmol) was added to a solution of 3,4-dimethyl-7,8,9,10-tetrahydro-6*H*-pyrido[3',4':4,5]imidazo[1,2-*a*][1,4]diazepin-1-amine dihydrochloride (400 mg, 1.31 mmol) and triethylamine (350 mg, 3.46 mmol) in DMF (250 mL) and stirred overnight at ambient temperature. The reaction mixture was concentrated under reduced pressure and adsorbed onto silica gel. The material was purified by column chromatography on silica gel, concentrated under reduced pressure, dissolved in dimethyl sulfoxide (DMSO), and purified by reverse phase prep HPLC

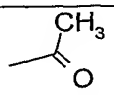
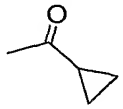
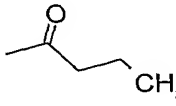
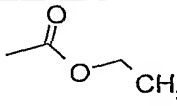
(eluting with 0.5% formic acid in water/0.5% formic acid in acetonitrile in a 10-minute gradient from 5:95 to 95:5) using a HPLC purification system obtained from Shimadzu corporation (based in Kyoto, Japan) to afford 135 mg of 3,4-dimethyl-9-(methylsulfonyl)-7,8,9,10-tetrahydro-6*H*-pyrido[3',4':4,5]imidazo[1,2-*a*][1,4]diazepin-1-amine. HRMS (EI) calcd for $C_{13}H_{19}N_5O_2S$ 310.1338, found 310.1346.

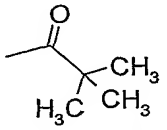
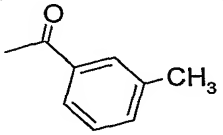
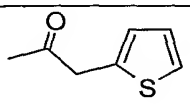
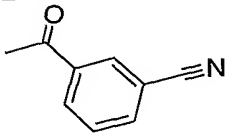
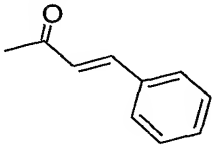
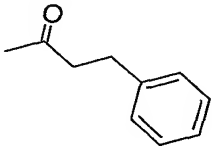
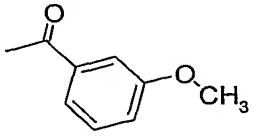
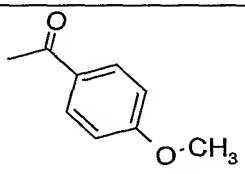
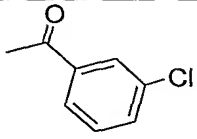
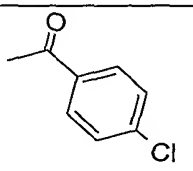
Examples 496 - 565

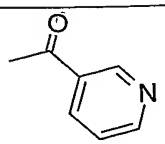
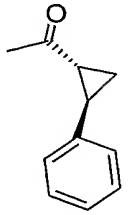
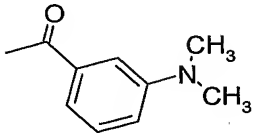
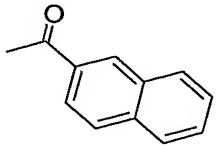
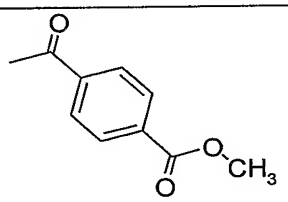
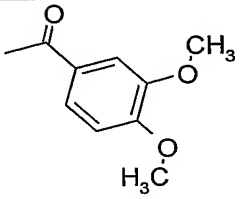
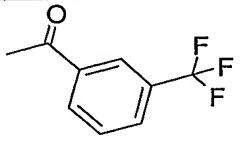
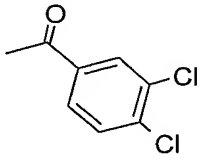
The methods described in Part C of Examples 435-450 were used to treat 3,4-dimethyl-7,8,9,10-tetrahydro-6*H*-pyrido[3',4':4,5]imidazo[1,2-*a*][1,4]diazepin-1-amine dihydrochloride (31 mg, 0.10 mmol) with *N,N*-diisopropylethylamine (0.057 mL, 0.33 mmol) and a reagent (0.12 mmol) indicated in the table below and purify the final compound. The table below shows the acid chloride, sulfonyl chloride, isocyanate, or carbamoyl chloride used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

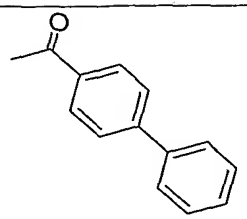
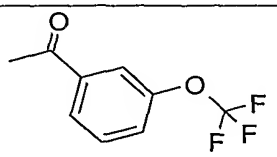
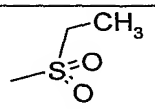
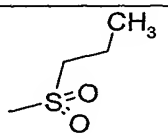
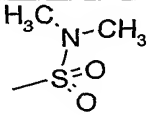
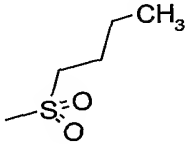
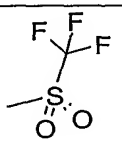
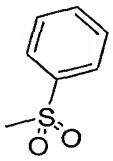
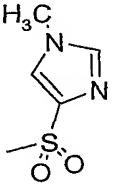
Examples 496 - 565

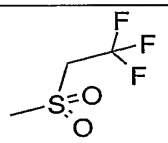
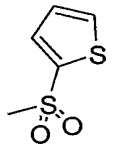
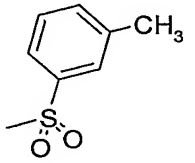
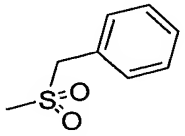
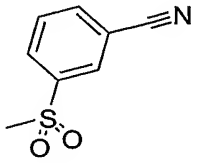
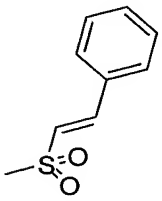
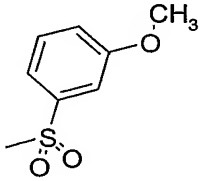
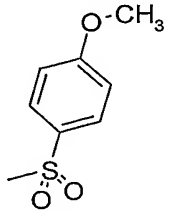


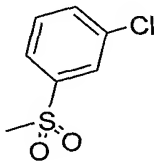
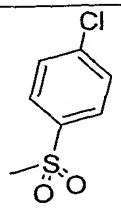
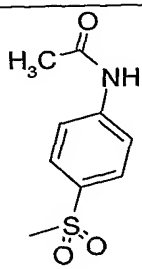
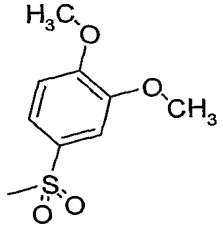
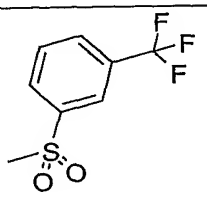
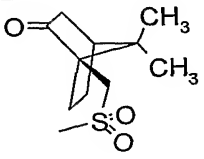
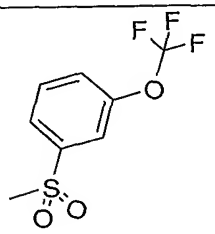
Example	Reagent	R	Measured Mass (M+H)
496	Acetyl chloride		274.1660
497	Cyclopropanecarbonyl chloride		300.1826
498	Butyryl chloride		302.1972
499	Ethyl chloroformate		304.1783

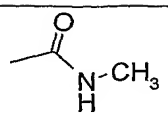
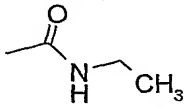
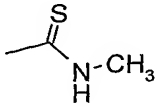
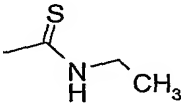
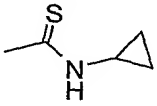
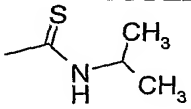
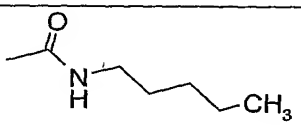
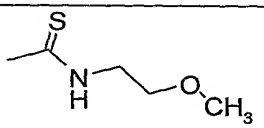
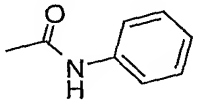
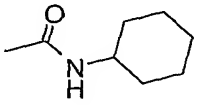
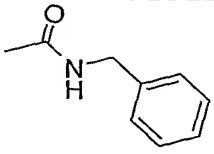
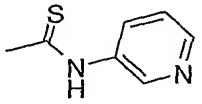
500	Pivaloyl chloride		316.2132
501	*m*-Toluoyl chloride		350.1996
502	2-Thiopheneacetyl chloride		356.1564
503	3-Cyanobenzoyl chloride		361.1768
504	Cinnamoyl chloride		362.1962
505	Hydrocinnamoyl chloride		364.2146
506	3-Methoxybenzoyl chloride		366.1923
507	*p*-Anisoyl chloride		366.1917
508	3-Chlorobenzoyl chloride		370.1443
509	4-Chlorobenzoyl chloride		370.1463

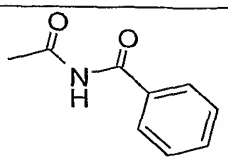
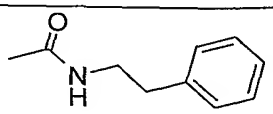
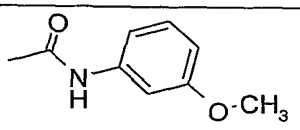
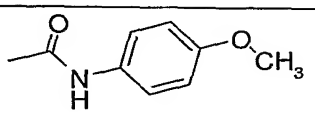
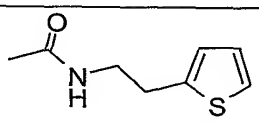
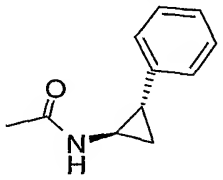
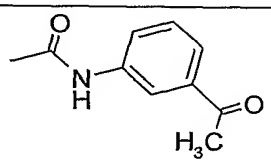
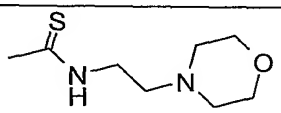
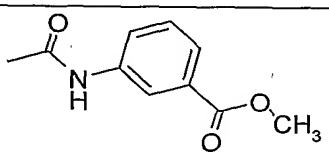
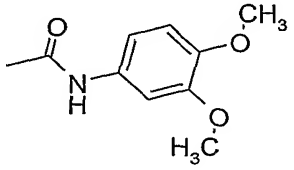
510	Nicotinoyl chloride hydrochloride		337.1793
511	*trans*-2-Phenyl-1-cyclopropanecarbonyl chloride		376.2150
512	3-Dimethylaminobenzoyl chloride		379.2267
513	2-Naphthoyl chloride		386.1989
514	Methyl 4-Chlorocarbonylbenzoate		394.1897
515	3,4-Dimethoxybenzoyl chloride		396.2018
516	3-(Trifluoromethyl)benzoyl chloride		404.1696
517	3,4-Dichlorobenzoyl chloride		404.1085

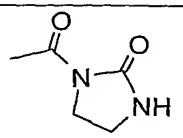
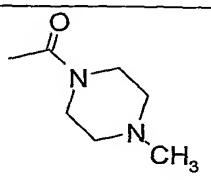
518	4-Biphenylcarbonyl chloride		412.2153
519	3-(Trifluoromethoxy)benzoyl chloride		420.1664
520	Ethanesulfonyl chloride		324.1501
521	1-Propanesulfonyl chloride		338.1653
522	Dimethylsulfamoyl chloride		339.1638
523	1-Butanesulfonyl chloride		352.1808
524	Trifluoromethanesulfonyl chloride		364.1060
525	Benzenesulfonyl chloride		372.1515
526	1-Methylimidazole-4-sulfonyl chloride		376.1573

527	2,2,2-Trifluoroethanesulfonyl chloride		378.1219
528	2-Thiophenesulfonyl chloride		378.1049
529	3-Methylbenzenesulfonyl chloride		386.1676
530	*alpha*-Toluenesulfonyl chloride		386.1669
531	3-Cyanobenzenesulfonyl chloride		397.1472
532	*beta*-Styrenesulfonyl chloride		398.1616
533	3-Methoxybenzenesulfonyl chloride		402.1617
534	4-Methoxybenzenesulfonyl chloride		402.1595

535	3-Chlorobenzenesulfonyl chloride		406.1125
536	4-Chlorobenzenesulfonyl chloride		406.1129
537	*N*-Acetylsulfanilyl chloride		429.1713
538	3,4-Dimethoxybenzenesulfonyl chloride		432.1721
539	3-(Trifluoromethyl)benzenesulfonyl chloride		440.1339
540	10-Camphorsulfonyl chloride		446.2263
541	3-(Trifluoromethoxy)benzenesulfonyl chloride		456.1322

542	Methyl isocyanate		289.1754
543	Ethyl isocyanate		303.1916
544	Methyl isothiocyanate		305.1573
545	Ethyl isothiocyanate		319.1732
546	Cyclopropyl isothiocyanate		331.1716
547	Isopropyl isothiocyanate		333.1890
548	Pentyl isocyanate		345.2412
549	2-Methoxyethyl isothiocyanate		349.1807
550	Phenyl isocyanate		351.1964
551	Cyclohexyl isocyanate		357.2403
552	Benzyl isocyanate		365.2083
553	3-Pyridyl isothiocyanate		368.1655

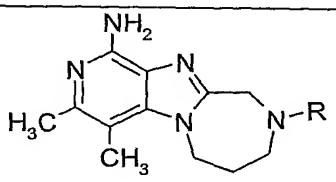
554	Benzoyl isocyanate		379.1888
555	2-Phenyl ethylisocyanate		379.2258
556	3-Methoxyphenyl isocyanate		381.2032
557	4- Methoxyphenyl isocyanate		381.2055
558	2-(Thien-2-yl)ethyl isocyanate		385.1847
559	*trans*-2-Phenylcyclopropyl isocyanate		391.2245
560	3-Acetylphenyl isocyanate		393.2043
561	2-Morpholinoethyl isothiocyanate		404.2240
562	3-Carbomethoxyphenyl isocyanate		409.1996
563	3,4-Dimethoxyphenyl isocyanate		411.2150

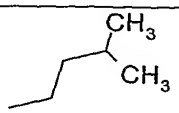
564	2-Oxo-1-imidazolidinecarbonyl chloride		344.1848
565	4-Methyl-1-piperazinecarbonyl chloride		358.2361

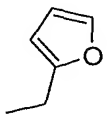
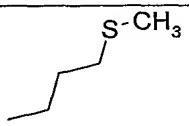
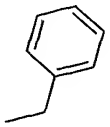
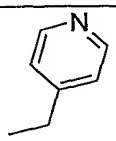
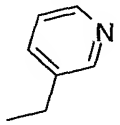
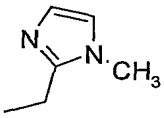
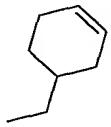
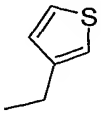
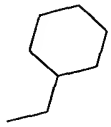
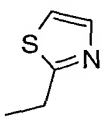
Examples 566 - 610

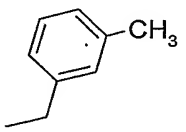
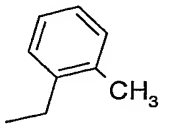
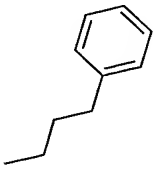
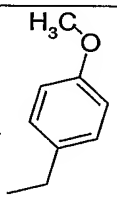
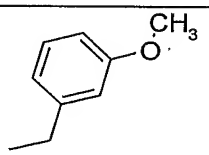
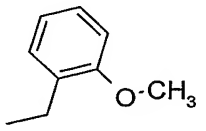
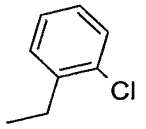
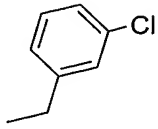
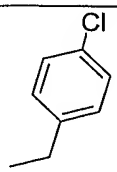
An aldehyde or ketone (0.12 mmol) indicated in the table below was added to a solution of 3,4-dimethyl-7,8,9,10-tetrahydro-6*H*-pyrido[3',4':4,5]imidazo[1,2-*a*][1,4]diazepin-1-amine dihydrochloride (30 mg, 0.10 mmol) and *N,N*-diisopropylethylamine (0.052 mL, 0.30 mmol) in anhydrous DMF (2 mL) in a test tube. The test tube was capped and shaken for 30 minutes. Borane-pyridine complex (13 μL, 0.104 mmol) was added, and the reaction was shaken overnight. The solvent was removed by vacuum centrifugation. The compounds were purified by prep HPLC according to the method described in Examples 370-385. The table below shows the aldehyde or ketone used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

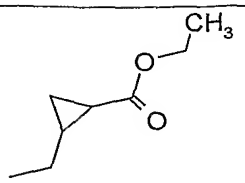
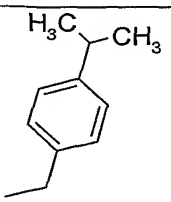
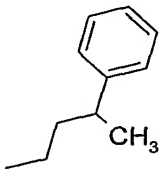
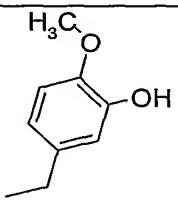
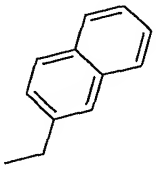
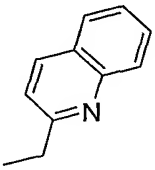
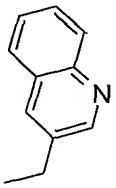
Examples 566 - 610

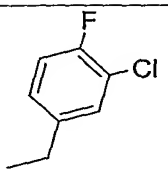
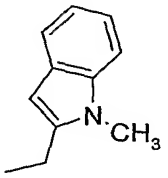
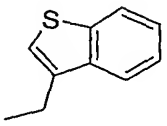
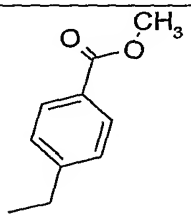
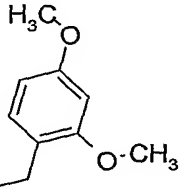
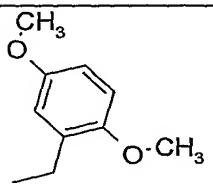
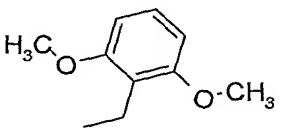
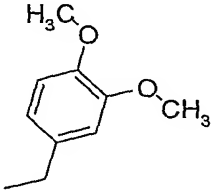


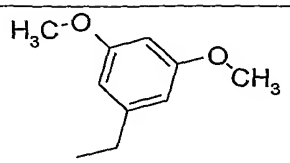
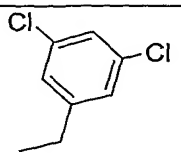
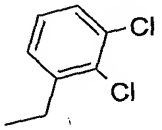
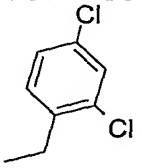
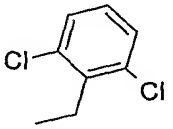
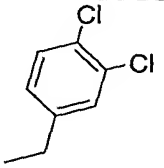
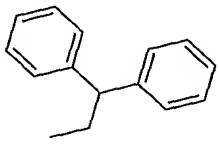
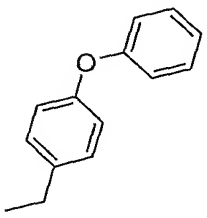
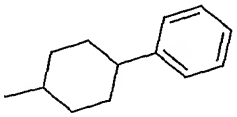
Example	Reagent	R	Measured Mass (M+H)
566	Cyclopropanecarboxaldehyde		286.2057
567	Isovaleraldehyde		302.2336

568	Furfural		312.1828
569	Methional		320.1927
570	Benzaldehyde		322.2043
571	Isonicotinaldehyde		323.1975
572	Nicotinaldehyde		323.1997
573	1-Methyl-2-imidazolecarboxaldehyde		326.2094
574	3-Cyclohexene-1-carboxaldehyde		326.2329
575	3-Thiophenecarboxaldehyde		328.1612
576	Cyclohexanecarboxaldehyde		328.2493
577	2-Thiazolecarboxaldehyde		329.1556

578	*m*-Tolualdehyde		336.2208
579	*o*-Tolualdehyde		336.2192
580	3-Phenylpropionaldehyde		350.2344
581	*p*-Anisaldehyde		352.2136
582	3-Methoxybenzaldehyde		352.2128
583	*o*-Anisaldehyde		352.2133
584	2-Chlorobenzaldehyde		356.1648
585	3-Chlorobenzaldehyde		356.1658
586	4-Chlorobenzaldehyde		356.1665

587	Ethyl 2-formyl-1-cyclopropanecarboxylate		358.2217
588	Cuminaldehyde		364.2509
589	3-Phenyl butanal		364.2505
590	3-Hydroxy-4-methoxybenzaldehyde		368.2104
591	2-Naphthaldehyde		372.2210
592	2-Quinolinecarboxaldehyde		373.2148
593	Quinoline-3-carboxaldehyde		373.2153

594	3-Chloro-4-fluorobenzaldehyde		374.1564
595	1-Methylindole-2-carboxaldehyde		375.2305
596	1-Benzothiophene-3-carbaldehyde		378.1757
597	Methyl 4-formylbenzoate		380.2109
598	2,4-Dimethoxybenzaldehyde		382.2269
599	2,5-Dimethoxybenzaldehyde		382.2254
600	2,6-Dimethoxybenzaldehyde		382.2229
601	3,4-Dimethoxybenzaldehyde		382.2260

602	3,5-Dimethoxybenzaldehyde		382.2259
603	3,5-Dichlorobenzaldehyde		390.1262
604	2,3-Dichlorobenzaldehyde		390.1270
605	2,4-Dichlorobenzaldehyde		390.1254
606	2,6-Dichlorobenzaldehyde		390.1268
607	3,4-Dichlorobenzaldehyde		390.1260
608	Diphenylacetaldehyde		412.2508
609	4-Phenoxybenzaldehyde		414.2299
610	4-Phenylcyclohexanone		390.2678

Examples 611 - 644

Part A

tert-Butyl 2-[(3-amino-5,6-dimethyl-2-phenoxypyridin-4-yl)amino]ethylcarbamate (17.9 g, 48.1 mmol), prepared as described in U.S. Patent No. 6,545,016 Example 23, Parts A through C, was dissolved in chloroform (250 mL). Ethyl 2-chloroacetimidate hydrochloride (15.2 g, 96 mmol) was added to the solution and the reaction mixture was stirred at 60 °C for 5 hours. Additional ethyl 2-chloroacetimidate hydrochloride (1.9 g) was added to the reaction mixture and stirred for 0.5 hours. The reaction mixture was cooled and filtered. The filtrate was diluted with chloroform (250 mL), washed with brine (2 x 300 mL), and the layers were separated. The combined organics were dried over magnesium sulfate, filtered with CELITE filter aid, and concentrated under reduced pressure. The material was recrystallized and filtered from acetonitrile to yield 13.28 g of *tert*-butyl 2-[2-(chloromethyl)-6,7-dimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl]ethylcarbamate as a white solid.

Part B

tert-Butyl 2-[2-(chloromethyl)-6,7-dimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl]ethylcarbamate (5.0 g, 11.6 mmol) was dissolved in THF (50 mL) and dichloromethane (50 mL) and cooled to 0 °C. Potassium *tert*-butoxide (17.0 mL of a 1 M solution in THF) was added and the reaction mixture was heated to 60 °C and stirred for two hours. The reaction mixture was concentrated under reduced pressure to afford 6.38 g of a light brown solid. The material was purified by column chromatography on silica gel (eluting with 98:2 methanol:dichloromethane) to afford 3.7 g of material.

Part C

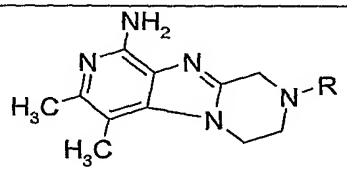
The material from Part B and ammonium acetate (28.1 g, 365 mmol) were placed in a sealed glass container and heated to 150 °C for 48 hours. The reaction mixture was cooled and dissolved in ethanol (100 mL). Hydrochloric acid (45 mL, 12 M) was added to the reaction mixture and stirred at 90 °C and stirred overnight. The mixture was cooled to ambient temperature and filtered. The filtrate was concentrated under reduced pressure to afford 8.8 g of an orange solid. The solid was washed with acetone and the filtrate was

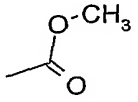
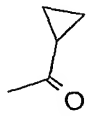
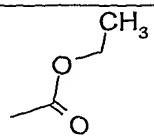
concentrated under reduced pressure to afford 3.32 of 3,4-dimethyl-6,7,8,9-tetrahydropyrido[3',4':4,5]imidazo[1,2-*a*]pyrazin-1-amine dihydrochloride as a yellow solid.

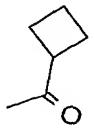
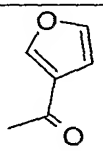
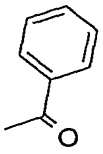
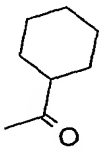
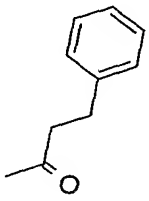
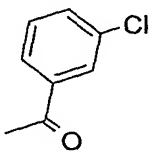
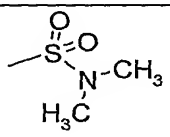
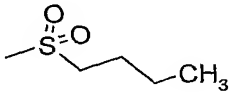
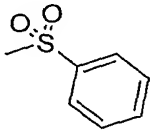
Part D

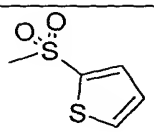
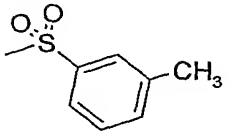
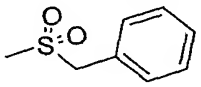
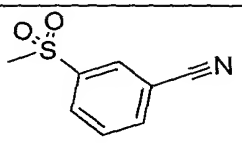
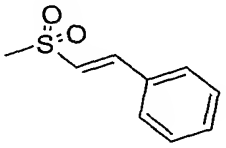
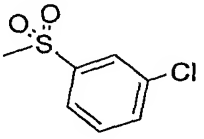
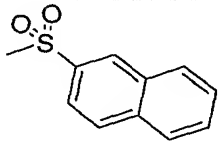
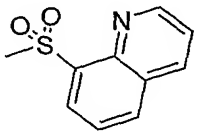
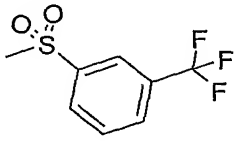
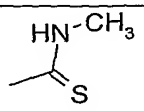
A reagent (0.11 mmol) from the table below was added to a test tube containing 3,4-dimethyl-6,7,8,9-tetrahydropyrido[3',4':4,5]imidazo[1,2-*a*]pyrazin-1-amine dihydrochloride (29 mg, 0.10 mmol) and *N,N*-diisopropylethylamine (0.058 mL, 0.33 mmol) in DMF (1 mL). The test tubes were capped and shaken overnight at ambient temperature. The reaction mixture was then purified using a Waters OASIS Sample Extractions Cartridge MCX followed by prep HPLC according to the methods described in Examples 370-385. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated product.

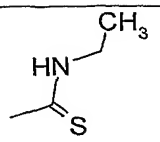
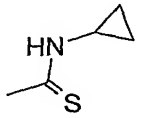
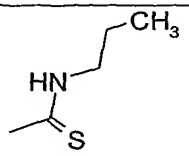
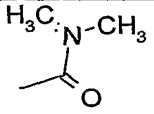
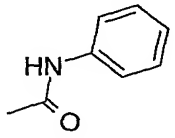
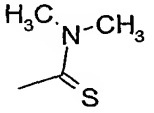
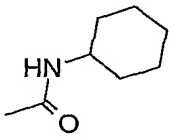
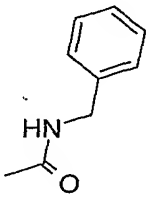
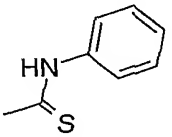
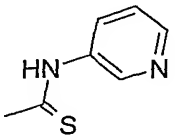
Example 611 - 644

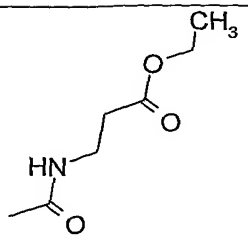


Example	Reagent	R	Measured Mass (M+H)
611	None		218.1400
612	Methyl chloroformate		276.1437
613	Cyclopropanecarbonyl chloride		286.1640
614	Ethyl chloroformate		290.1594

615	Cyclobutanecarbonyl chloride		300.1812
616	3-Furoyl chloride		312.1445
617	Benzoyl chloride		322.1657
618	Cyclohexanecarbonyl chloride		328.2118
619	Hydrocinnamoyl chloride		350.1960
620	3-Chlorobenzoyl chloride		356.1270
621	Dimethylsulfamoyl chloride		325.1447
622	1-Butanesulfonyl chloride		338.1628
623	Benzenesulfonyl chloride		358.1319

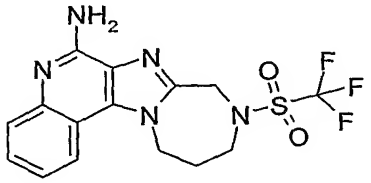
624	2-Thiophenesulfonyl chloride		364.0906
625	3-Methylbenzenesulfonyl chloride		372.1490
626	*alpha*-Toluenesulfonyl chloride		372.1510
627	3-Cyanobenzenesulfonyl chloride		383.1274
628	*beta*-Styrenesulfonyl chloride		384.1471
629	3-Chlorobenzenesulfonyl chloride		392.0962
630	2-Naphthalenesulfonyl chloride		408.1496
631	8-Quinolinesulfonyl chloride		409.1413
632	3-(Trifluoromethyl)benzenesulfonyl chloride		426.1242
633	Methyl isothiocyanate		291.1377

634	Ethyl isothiocyanate		305.1537
635	Cyclopropyl isothiocyanate		317.1536
636	n-Propyl isothiocyanate		319.1671
637	*N,N*-Dimethylcarbamoyl chloride		289.1757
638	Phenyl isocyanate		337.1766
639	Dimethylthiocarbamoyl chloride		305.1553
640	Cyclohexyl isocyanate		343.2225
641	Benzyl isocyanate		351.1924
642	Phenyl isothiocyanate		353.1539
643	3-Pyridyl isothiocyanate		354.1503

644	Ethyl 3-isocyanatopropionate		361.1996

Example 645

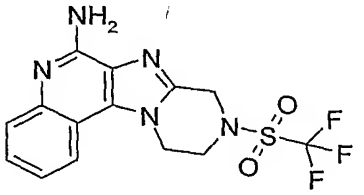
9-[(Trifluoromethyl)sulfonyl]-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine



The methods described in Example 8 can be used to prepare 9-[(trifluoromethyl)sulfonyl]-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine from *tert*-butyl 11,12-dihydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(10*H*)-carboxylate using trifluoromethanesulfonyl chloride in lieu of methanesulfonyl chloride in Part C.

Example 646

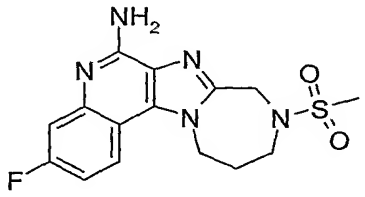
9-[(Trifluoromethyl)sulfonyl]-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine



A modification of the methods described in Example 5 can be used to prepare 9-[(trifluoromethyl)sulfonyl]-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine from *tert*-butyl 6-amino-10,11-dihydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(8*H*)-carboxylate using trifluoromethanesulfonyl chloride in lieu of methanesulfonyl chloride in Part B. Normal phase prep HPLC may be used in Part B to purify the product.

Example 647

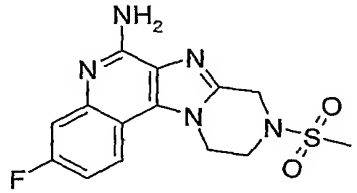
3-Fluoro-9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine



The methods described in Parts A through D of Example 368 and Parts A through G of Example 369 can be used to prepare 3-fluoro-9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine using 3-fluoroaniline in lieu of 3-benzyloxyaniline in Part A of Example 368.

Example 648

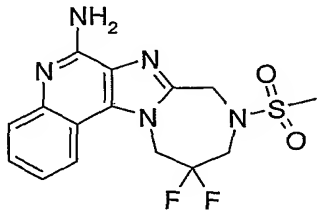
3-Fluoro-9-(methylsulfonyl)-8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine



The methods described in Parts A through K of Example 368 can be used to prepare 3-fluoro-9-(methylsulfonyl)- 8,9,10,11-tetrahydropyrazino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine using 3-fluoroaniline in lieu of 3-benzyloxyaniline in Part A of Example 368.

Example 649

11,11-Difluoro-9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine



Part A

The method described in Part B of Example 364 can be used to prepare *tert*-butyl 3-amino-2,2-difluoropropylcarbamate from 2,2-difluropropane-1,3-diamine, which is available from the literature procedure: Nanjappan, P. et al., *Tetrahedron 50*(29), pp. 8617-8632, (1994).

Part B

The methods described in Parts A through D of Example 6 can be used to prepare *tert*-butyl 11,11-difluoro-11,12-dihydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(10*H*)-carboxylate, using *tert*-butyl 3-amino-2,2-difluoropropylcarbamate in lieu of *tert*-butyl 3-aminopropylcarbamate in Part A.

Part C

The methods described in Example 364 can be used to prepare 11,11-difluoro-9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine using *tert*-butyl 11,11-difluoro-11,12-dihydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(10*H*)-carboxylate in lieu of *tert*-butyl 11,12-dihydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinoline-9(10*H*)-carboxylate in Part A.

Compounds of the invention were found to induce or inhibit cytokine biosynthesis when tested using the methods described below.

CYTOKINE INDUCTION IN HUMAN CELLS

Compounds of the invention have been found to modulate cytokine biosynthesis by inducing the production of interferon α and/or tumor necrosis factor α when tested using the method described below. Particular examples include, but are not limited to, the compounds of Examples 1-5, 7-10, 12-14, 16, 19, 20, 22, 24-26, 28, 34, 37, 39, 41, 43, 44, 46, 74, 77-79, 81-84, 87, 92, 93, 97-100, 103, 106, 109, 112, 114, 115, 117, 121, 123, 125, 127-133, 135, 136, 138, 140, 147, 153, 157, 159, 160, 189-191, 193, 195-198, 200, 202-205, 208, 216, 217, 223, 230, 231, 239, 264, 266, 282, 283, 285-289, 296, 297, 302, 308, 309, 313, 345, 362-369, 386, 388, 389, 391-394, 396, 399, 404, 412, 413, 439, 440, 470, 485, 488-491, 493, 497, 498, 500, 567, 612, 625, 626, 631, 635-639, 641, and 644.

An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon (α) and tumor necrosis factor (α) (IFN and TNF, respectively) secreted into culture media as described by Testerman et al. in "Cytokine Induction by the Immunomodulators Imiquimod and S-27609", *Journal of Leukocyte Biology*, *58*, 365-372 (September, 1995).

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into EDTA vacutainer tubes. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077. Blood is diluted 1:1 with Dulbecco's Phosphate Buffered Saline (DPBS) or Hank's Balanced Salts Solution (HBSS). The PBMC layer is collected and washed twice with DPBS or HBSS and resuspended at 4 x 10^6 cells/mL in RPMI complete. The PBMC suspension is added to 48 well flat bottom sterile tissue culture plates (Costar, Cambridge, MA or Becton Dickinson Labware, Lincoln Park, NJ) containing an equal volume of RPMI complete media containing test compound.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. The compounds are generally tested at concentrations ranging from 30-0.014 μM.

Incubation

The solution of test compound is added at 60 μM to the first well containing RPMI complete and serial 3 fold dilutions are made in the wells. The PBMC suspension is then added to the wells in an equal volume, bringing the test compound concentrations to the desired range (30-0.014 μM). The final concentration of PBMC suspension is 2×10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 x g) at 4°C. The cell-free culture supernatant is removed with a sterile polypropylene pipet and transferred to sterile polypropylene tubes. Samples are maintained at –30 to -70°C until analysis. The samples are analyzed for interferon (α) by ELISA and for tumor necrosis factor (α) by ELISA or IGEN Assay.

Interferon (α) and Tumor Necrosis Factor (α) Analysis by ELISA

Interferon (α) concentration is determined by ELISA using a Human Multi-Species kit from PBL Biomedical Laboratories, New Brunswick, NJ. Results are expressed in pg/mL.

Tumor necrosis factor (α) (TNF) concentration is determined using ELISA kits available from Biosource International, Camarillo, CA. Alternately, the TNF concentration can be determined by ORIGEN M-Series Immunoassay and read on an IGEN M-8 analyzer from IGEN International, Gaithersburg, MD. The immunoassay uses a human TNF capture and detection antibody pair from Biosource International, Camarillo, CA. Results are expressed in pg/mL.

TNF-α INHIBITION IN MOUSE CELLS

Certain compounds of the invention may modulate cytokine biosynthesis by inhibiting production of tumor necrosis factor α (TNF-α) when tested using the method described below. Particular examples, include but are not limited to, the compounds of Examples 74-76, 79, 81, 92, 94, 95, 103, 104, 108-110, 200, 210, 212-218, 220-226, 230,

232-234, 236-240, 242-244, 283, 285-290, 293, 299, 301-305, 308, 310-312, 314, 315, 317, 321, 323, 324, and 326-328.

The mouse macrophage cell line Raw 264.7 is used to assess the ability of compounds to inhibit tumor necrosis factor-α (TNF-α) production upon stimulation by lipopolysaccharide (LPS).

Single Concentration Assay:

Blood Cell Preparation for Culture

Raw cells (ATCC) are harvested by gentle scraping and then counted. The cell suspension is brought to 3 x 10^5 cells/mL in RPMI with 10 % fetal bovine serum (FBS). Cell suspension (100 µL) is added to 96-well flat bottom sterile tissues culture plates (Becton Dickinson Labware, Lincoln Park, NJ). The final concentration of cells is 3 x 10^4 cells/well. The plates are incubated for 3 hours. Prior to the addition of test compound the medium is replaced with colorless RPMI medium with 3 % FBS.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. Compounds are tested at 5µM. LPS (Lipopolysaccaride from *Salmonella typhimurium*, Sigma-Aldrich) is diluted with colorless RPMI to the EC_{70} concentration as measured by a dose response assay.

Incubation

A solution of test compound (1µl) is added to each well. The plates are mixed on a microtiter plate shaker for 1 minute and then placed in an incubator. Twenty minutes later the solution of LPS (1 µL, EC_{70} concentration ~ 10 ng/ml) is added and the plates are mixed for 1 minute on a shaker. The plates are incubated for 18 to 24 hours at 37 °C in a 5 % carbon dioxide atmosphere.

TNF-α Analysis

Following the incubation the supernatant is removed with a pipet. TNF-α concentration is determined by ELISA using a mouse TNF- α kit (from Biosource

International, Camarillo, CA). Results are expressed in pg/mL. TNF-α expression upon LPS stimulation alone is considered a 100% response.

Dose Response Assay:

Blood Cell Preparation for Culture

Raw cells (ATCC) are harvested by gentle scraping and then counted. The cell suspension is brought to 4 x 10^5 cells/mL in RPMI with 10 % FBS. Cell suspension (250 μL) is added to 48-well flat bottom sterile tissues culture plates (Costar, Cambridge, MA). The final concentration of cells is 1 x 10^5 cells/well. The plates are incubated for 3 hours. Prior to the addition of test compound the medium is replaced with colorless RPMI medium with 3 % FBS.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. Compounds are tested at 0.03, 0.1, 0.3, 1, 3, 5 and 10 μM. LPS (Lipopolysaccaride from *Salmonella typhimurium*, Sigma-Aldrich) is diluted with colorless RPMI to the EC_{70} concentration as measured by dose response assay.

Incubation

A solution of test compound (200 μl) is added to each well. The plates are mixed on a microtiter plate shaker for 1 minute and then placed in an incubator. Twenty minutes later the solution of LPS (200 μL, EC_{70} concentration ~ 10 ng/ml) is added and the plates are mixed for 1 minute on a shaker. The plates are incubated for 18 to 24 hours at 37 °C in a 5 % carbon dioxide atmosphere.

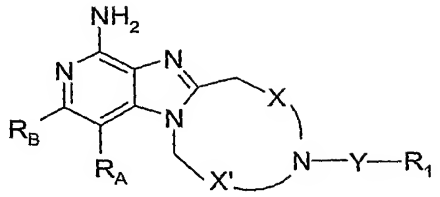
TNF-α Analysis

Following the incubation the supernatant is removed with a pipet. TNF-α concentration is determined by ELISA using a mouse TNF- α kit (from Biosource International, Camarillo, CA). Results are expressed in pg/mL. TNF-α expression upon LPS stimulation alone is considered a 100% response.

The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. It should be understood that this invention is not intended to be unduly limited by the illustrative embodiments and examples set forth herein and that such examples and embodiments are presented by way of example only with the scope of the invention intended to be limited only by the claims set forth herein as follows.

What we claim is:

1. A compound of the Formula I:



I

wherein:

R_A and R_B are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

or when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R' groups;

or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

X is a bond or a straight or branched chain C_{1-2} alkylene;

X' is a straight or branched chain C_{1-8} alkylene optionally substituted with hydroxy, $-O-R_{11}$, or one or more halogen atoms wherein the hydroxy, $-O-R_{11}$, or one or more halogen atoms are bonded to a carbon atom other than a carbon atom adjacent to a nitrogen atom;

X and X' are further characterized in that the total number of ring carbon atoms contributed by X and X' is 1 to 3;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-C(R_6)-N(R_8)-$,

$-C(R_6)-N(R_8)-C(R_6)-$, and

$-C(R_6)-N(R_8)-S(O)_2-$;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_1 is selected from the group consisting of: hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, alkanoyl, alkanoyloxy, alkoxycarbonyl, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylthio, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, and in the case of aryl, methylenedioxy; further with the proviso that when R_A and R_B together form a fused benzene ring that is unsubstituted or substituted by C_{1-4} alkyl, C_{1-4} alkoxy, or halogen, and Y is a bond, R_1 is not hydrogen or C_{1-4} alkyl;

R_6 is selected from the group consisting of =O and =S;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

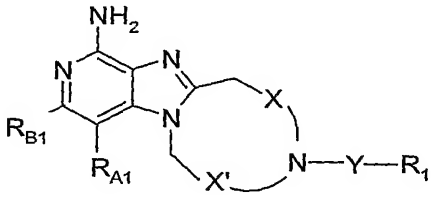
R_9 is selected from the group consisting of hydrogen and alkyl;

R_{11} is selected from the group consisting of C_{1-6} alkyl and $-Si(C_{1-6}$ alkyl$)_3$; and

R' is a non-interfering substituent;

or a pharmaceutically acceptable salt thereof.

2. A compound of the Formula II:



II

wherein:

R_{A1} and R_{B1} are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

or when taken together, R_{A1} and R_{B1} form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group;

or when taken together, R_{A1} and R_{B1} form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

X is a bond or a straight or branched chain C_{1-2} alkylene;

X' is a straight or branched chain C_{1-8} alkylene optionally substituted with hydroxy, -O-R_{11}, or one or more halogen atoms wherein the hydroxy, -O-R_{11}, or one or more halogen atoms are bonded to a carbon atom other than a carbon atom adjacent to a nitrogen atom;

X and X' are further characterized in that the total number of ring carbon atoms contributed by X and X' is 1 to 3;

Y is selected from the group consisting of:

a bond,

-$S(O)_2$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-$C(R_6)$-$N(R_8)$-,

-$C(R_6)$-$N(R_8)$-$C(R_6)$-, and

-$C(R_6)$-$N(R_8)$-$S(O)_2$-;

R_1 is selected from the group consisting of: hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, alkanoyl, alkanoyloxy, alkoxycarbonyl, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylthio, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, and in the case of aryl, methylenedioxy; further with the proviso that when R_{A1} and R_{B1} together form a fused benzene ring that is unsubstituted or substituted by C_{1-4} alkyl, C_{1-4} alkoxy, or halogen, and Y is a bond, R_1 is not hydrogen or C_{1-4} alkyl;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_3 is selected from the group consisting of:

$-Z-R_4$,

$-Z-X''-R_4$,

$-Z-X''-Y'-R_4$,

$-Z-X''-Y'-X''-Y'-R_4$, and

$-Z-X''-R_5$;

X'' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y' is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

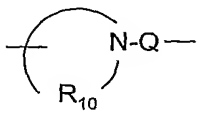
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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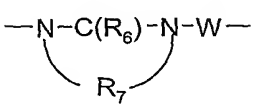

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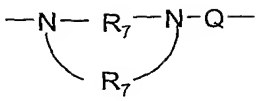
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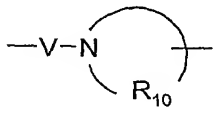
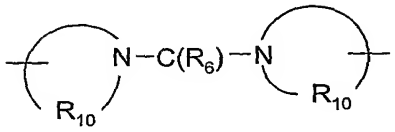
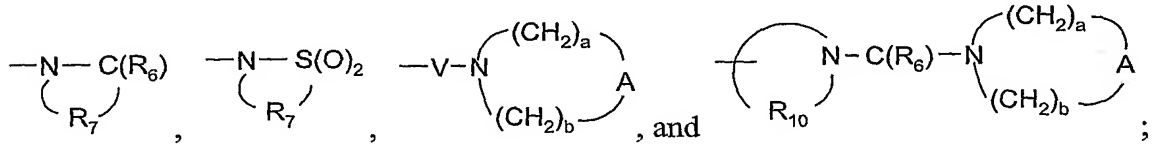

, and


;

Z is a bond or -O-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of


;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

R_{11} is selected from the group consisting of C_{1-6} alkyl and $-Si(C_{1-6}$ alkyl$)_3$;

A is selected from the group consisting of $-CH_2$-, -O-, -C(O)-, -S(O)$_{0-2}$-, and

$-N(R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)$;

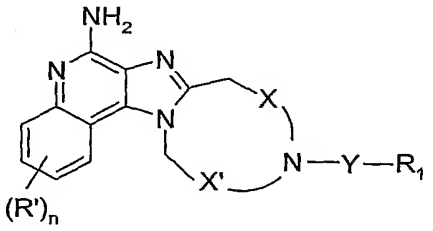
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

3. A compound of the Formula III:



III

wherein:

X is a bond or a straight or branched chain C_{1-2} alkylene;

X' is a straight or branched chain C_{1-8} alkylene optionally substituted with hydroxy wherein the hydroxy is bonded to a carbon atom other than a carbon atom adjacent a nitrogen atom;

X and X' are further characterized in that the total number of ring carbon atoms contributed by X and X' is 1 to 3;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-N(R_8)-$,

$-C(R_6)-N(R_8)-C(R_6)-$, and

$-C(R_6)-N(R_8)-S(O)_2-$;

R_1 is selected from the group consisting of: hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, alkanoyl, alkanoyloxy, alkoxycarbonyl, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylthio, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, and in the case of aryl, methylenedioxy; further with the proviso that when Y is a bond, R_1 is not hydrogen or C_{1-4} alkyl;

R_6 is selected from the group consisting of =O and =S;

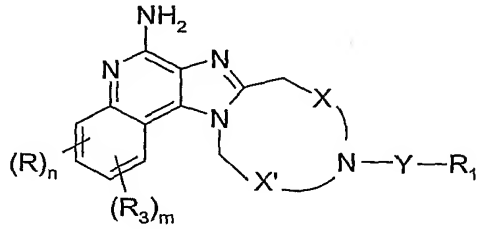
R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R' is a non-interfering substituent; and

n is an integer from 0 to 4;

or a pharmaceutically acceptable salt thereof.

4. A compound of the Formula IV:



IV

wherein:

X is a bond or a straight or branched chain C_{1-2} alkylene;

X' is a straight or branched chain C_{1-8} alkylene optionally substituted with hydroxy, -O-R_{11}, or one or more halogen atoms wherein the hydroxy, -O-R_{11}, or one or more

halogen atoms are bonded to a carbon atom other than a carbon atom adjacent to a nitrogen atom;

X and X' are further characterized in that the total number of ring carbon atoms contributed by X and X' is 1 to 3;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-C(R_6)-N(R_8)-$,

$-C(R_6)-N(R_8)-C(R_6)-$, and

$-C(R_6)-N(R_8)-S(O)_2-$;

R_1 is selected from the group consisting of: hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, alkanoyl, alkanoyloxy, alkoxycarbonyl, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylthio, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, and in the case of aryl, methylenedioxy;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_3 is selected from the group consisting of:

$-Z-R_4$,

$-Z-X''-R_4$,

$-Z-X''-Y'-R_4$,

$-Z-X''-Y'-X''-Y'-R_4$, and

$-Z-X''-R_5$;

m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1;

n is an integer from 0 to 4;

X'' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y' is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

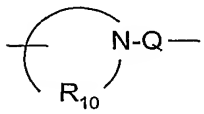
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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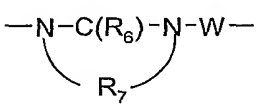

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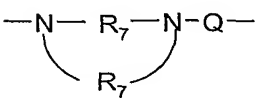

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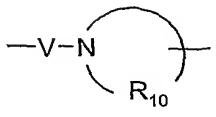
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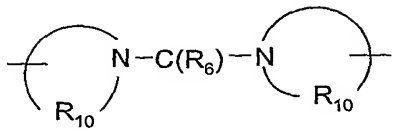
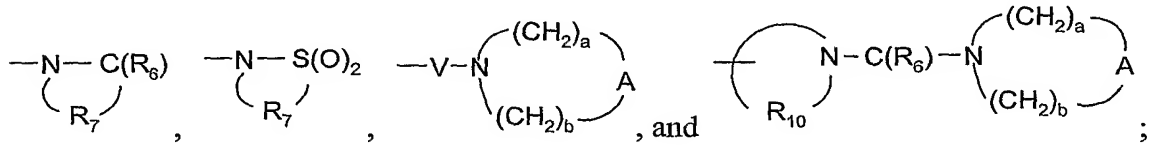

;

Z is a bond or -O-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of


;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

R_{11} is selected from the group consisting of C_{1-6} alkyl and $-Si(C_{1-6}\ alkyl)_3$;

A is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(R_6)-O-, and -C(R_6)-N(OR_9);

V is selected from the group consisting of -C(R_6)-, -O-C(R_6)-, -N(R_8)-C(R_6)-, and -S(O)$_2$-;

W is selected from the group consisting of a bond, -C(O)-, and –S(O)$_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

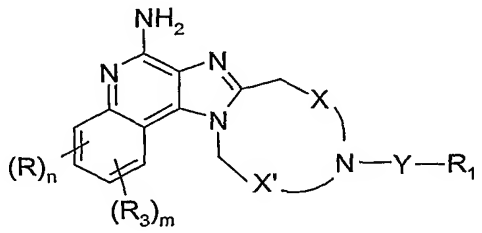
with the proviso that R_1 is not hydrogen or C_{1-4} alkyl when Y is a bond, and:

n and m are both 0, or

m is 0, n is 1, and R is selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, and halogen;

or a pharmaceutically acceptable salt thereof.

A compound of the Formula IV:



IV

wherein:

X is a bond or a straight or branched chain C_{1-2} alkylene;

X' is a straight or branched chain C_{1-8} alkylene optionally substituted with hydroxy wherein the hydroxy is bonded to a carbon atom other than a carbon atom adjacent a nitrogen atom;

X and X' are further characterized in that the total number of ring carbon atoms contributed by X and X' is 1 to 3;

Y is selected from the group consisting of:

a bond,

-S(O)$_2$-,

-S(O)$_2$-N(R_8)-,

-C(R_6)-,

-C(R_6)-N(R_8)-,

$-C(R_6)-N(R_8)-C(R_6)-$, and

$-C(R_6)-N(R_8)-S(O)_2-$;

R_1 is selected from the group consisting of: hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, alkanoyl, alkanoyloxy, alkoxycarbonyl, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylthio, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, and in the case of aryl, methylenedioxy; further with the proviso that when Y is a bond, R_1 is not hydrogen or C_{1-4} alkyl;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_3 is selected from the group consisting of:

$-Z-R_4$,

$-Z-X''-R_4$,

$-Z-X''-Y'-R_4$,

$-Z-X''-Y'-X''-Y'-R_4$, and

$-Z-X''-R_5$;

m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1;

n is an integer from 0 to 4;

X" is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y' is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

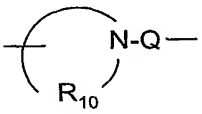
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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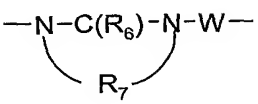

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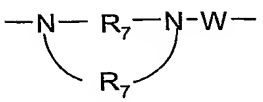

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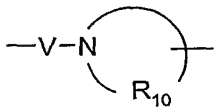

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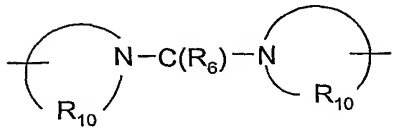


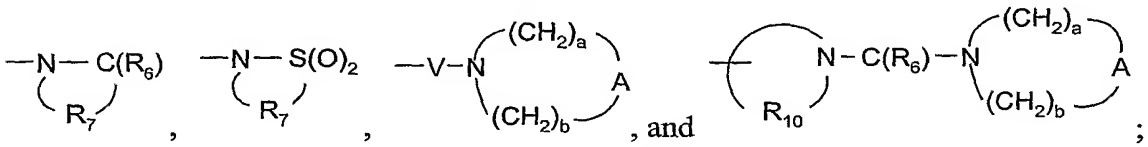
;

Z is a bond or -O-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl,

alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)$;

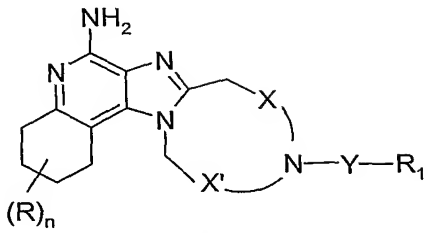
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

6. A compound of the Formula V:



V

wherein:

X is a bond or a straight or branched chain C_{1-2} alkylene;

X' is a straight or branched chain C_{1-8} alkylene optionally substituted with hydroxy, -O-R_{11}, or one or more halogen atoms wherein the hydroxy, -O-R_{11}, or one or more halogen atoms are bonded to a carbon atom other than a carbon atom adjacent to a nitrogen atom;

X and X' are further characterized in that the total number of ring carbon atoms contributed by X and X' is 1 to 3;

Y is selected from the group consisting of:

a bond,

-$S(O)_2$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-$C(R_6)$-$N(R_8)$-,

-$C(R_6)$-$N(R_8)$-$C(R_6)$-, and

-$C(R_6)$-$N(R_8)$-$S(O)_2$-;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_1 is selected from the group consisting of: hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, alkanoyl, alkanoyloxy, alkoxycarbonyl, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylthio, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, and in the case of aryl, methylenedioxy;

R_6 is selected from the group consisting of =O and =S;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

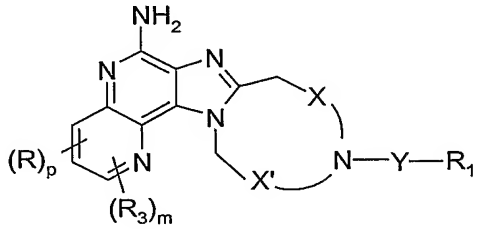
R_9 is selected from the group consisting of hydrogen and alkyl;

R_{11} is selected from the group consisting of C_{1-6} alkyl and $-Si(C_{1-6}$ alkyl$)_3$; and

n is an integer from 0 to 4;

or a pharmaceutically acceptable salt thereof.

7. A compound of the Formula VI:



VI

wherein:

X is a bond or a straight or branched chain C_{1-2} alkylene;

X' is a straight or branched chain C_{1-8} alkylene optionally substituted with hydroxy, $-O-R_{11}$, or one or more halogen atoms wherein the hydroxy, $-O-R_{11}$, or one or more

halogen atoms are bonded to a carbon atom other than a carbon atom adjacent to a nitrogen atom;

X and X' are further characterized in that the total number of ring carbon atoms contributed by X and X' is 1 to 3;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-C(R_6)-N(R_8)-$,

$-C(R_6)-N(R_8)-C(R_6)-$, and

$-C(R_6)-N(R_8)-S(O)_2-$;

R_1 is selected from the group consisting of: hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, alkanoyl, alkanoyloxy, alkoxycarbonyl, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylthio, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, and in the case of aryl, methylenedioxy;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_3 is selected from the group consisting of:

$-Z-R_4$,

$-Z-X''-R_4$,

$-Z-X''-Y'-R_4$,

$-Z-X''-Y'-X''-Y'-R_4$, and

$-Z-X''-R_5$;

X" is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y' is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

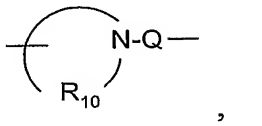
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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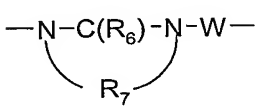

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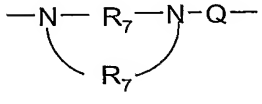

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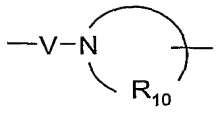
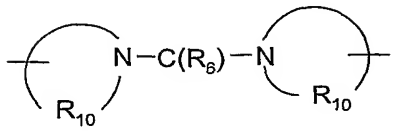
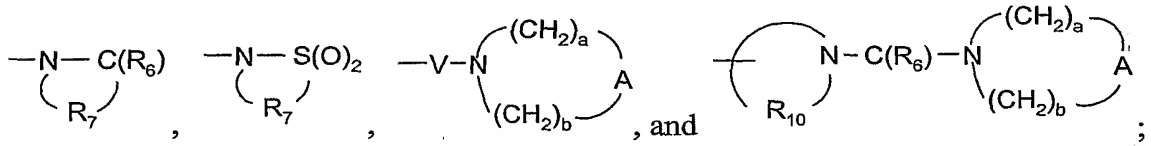

, and


;

Z is a bond or -O-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of


;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

R_{11} is selected from the group consisting of C_{1-6} alkyl and $-Si(C_{1-6}$ alkyl$)_3$;

A is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(R_6)-O-, and -C(R_6)-N(OR_9);

V is selected from the group consisting of -C(R_6)-, -O-C(R_6)-, -N(R_8)-C(R_6)-, and -S(O)$_2$-;

W is selected from the group consisting of a bond, -C(O)-, and –S(O)$_2$-;

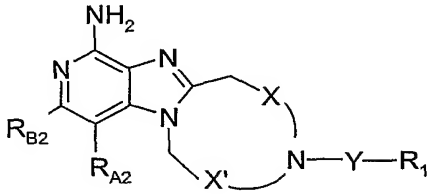
m is 0 or 1; with the proviso that when m is 1, then p is 0 or 1;

p is an integer from 0 to 3; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

8. A compound of the Formula VII:



VII

wherein:

R_{A2} and R_{B2} are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

X is a bond or a straight or branched chain C_{1-2} alkylene;

X' is a straight or branched chain C_{1-8} alkylene optionally substituted with hydroxy, -O-R_{11}, or one or more halogen atoms wherein the hydroxy, -O-R_{11}, or one or more halogen atoms are bonded to a carbon atom other than a carbon atom adjacent to a nitrogen atom;

X and X' are further characterized in that the total number of ring carbon atoms contributed by X and X' is 1 to 3;

Y is selected from the group consisting of:

a bond,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-C(R_6)-N(R_8)-$,

$-C(R_6)-N(R_8)-C(R_6)-$, and

$-C(R_6)-N(R_8)-S(O)_2-$;

R_1 is selected from the group consisting of: hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, alkanoyl, alkanoyloxy, alkoxycarbonyl, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylthio, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo, and in the case of aryl, methylenedioxy;

R_6 is selected from the group consisting of =O and =S;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl; and

R_{11} is selected from the group consisting of C_{1-6} alkyl and $-Si(C_{1-6}$ alkyl$)_3$;

or a pharmaceutically acceptable salt thereof.

9. A compound or salt as in any one of claims 3 through 6 wherein n is 0.

10. A compound or salt of claim 7 wherein p is 0.

11. A compound or salt as in any one of claims 2, 4, 5, 7, and 10 or claim 9 as dependent on claim 4 or claim 5 wherein R_3 is pyridyl, benzyloxy, or 3-pyrrolylpropoxy.

12. A compound or salt as in any one of claims 1, 2, and 4 through 7 wherein R is hydroxy.

13. A compound or salt as in any one of claims 4, 5, 7, and 10 or claim 9 as dependent on claim 4 or claim 5 wherein m is 0.

14. A compound or salt of claim 8 wherein R_{A2} and R_{B2} are each methyl.

15. A compound or salt as in any one of the preceding claims wherein Y is selected from the group consisting of –C(O)-, -$S(O)_2$-, or –C(O)-NH-, and R_1 is C_{1-3} alkyl.

16. A compound or salt as in any one of the preceding claims wherein Y is –$S(O)_2$-, and R_1 is methyl.

17. A compound or salt as in any one of claims 1 through 16 wherein X is a bond and X' contributes one ring carbon atom.

18. A compound or salt as in any one of claims 1 through 17 wherein X' is methylene.

19. A compound or salt as in any one of claims 1 through 16 wherein X is a bond and X' contributes two ring carbon atoms.

20. A compound or salt as in any one of claims 1 through 16 or claim 19 wherein X' is ethylene.

21. A compound or salt as in any one of claims 1 through 20 wherein the compound or salt induces the biosynthesis of one or more cytokines.

22. A compound or salt as in any one of claims 1 through 20 wherein the compound or salt inhibits the biosynthesis of TNF-α.

23. A compound or salt of as in any one of claims 1 through 5 wherein the compound is 9-(methylsulfonyl)-9,10,11,12-tetrahydro-8*H*-[1,4]diazepino[1',2':1,2]imidazo[4,5-*c*]quinolin-6-amine or a pharmaceutically acceptable salt thereof.

24. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of any one of the preceding claims in combination with a pharmaceutically acceptable carrier.

25. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of claim 21 or claim 23 to the animal or administering a pharmaceutical composition of claim 24 as dependent on claim 21 or claim 23 to the animal.

26. A method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of claim 21 or claim 23 to the animal or administering a pharmaceutical composition of claim 24 as dependent on claim 21 or claim 23 to the animal.

27. A method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of claim 21 or claim 23 to the animal or administering a pharmaceutical composition of claim 24 as dependent on claim 21 or claim 23 to the animal.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/043474

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/14 C07D471/22 A61K31/551 A61P31/12 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96/21663 A (MINNESOTA MINING AND MANUFACTURING COMPANY) 18 July 1996 (1996-07-18) Formula II, page 13, lines 17-22; claims 1,8; example 3	1-27
A	WO 02/46194 A (3M INNOVATIVE PROPERTIES COMPANY; LINDSTROM, KYLE J) 13 June 2002 (2002-06-13) Formula I, page 25, lines 1-14	1-27
A	US 6 541 485 B1 (CROOKS STEPHEN L ET AL) 1 April 2003 (2003-04-01) Formula I, column 14, line 38 - column 16, line 32	1-27

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 June 2005	20/06/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Rudolf, M

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/043474

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95/02597 A (MINNESOTA MINING AND MANUFACTURING COMPANY) 26 January 1995 (1995-01-26) Formula I, page 13, lines 5-20	1-27
A	WO 99/18105 A (ORTHO-MCNEIL PHARMACEUTICAL, INC) 15 April 1999 (1999-04-15) Formula I, page 3, lines 26-35	1-27

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/043474

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 25-27 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2004/043474

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
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